UNIVERSIDAD AUTÓNOMA DE MADRID

Facultad de Medicina

Tesis Doctoral

EVENTOS Y FACTORES DE RIESGO CARDIOVASCULAR EN PACIENTES CON PATOLOGÍA PSIQUIÁTRICA ATENDIDOS EN ATENCIÓN PRIMARIA

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INFORMAN:

Que Doña María Pérez- Piñar López ha realizado bajo su dirección el trabajo:

Eventos y factores de riesgo cardiovascular en pacientes con patología psiquiátrica atendidos en atención primaria.

Es un trabajo original, rigurosamente realizado, y es apto para ser presentado públicamente con el fin de obtener el grado de doctor.

Para que así conste y surta los efectos oportunos se firma este documento en Madrid el 25 de junio de 2017.

D Luis Ayerbe García-Monzón D Esteban González López

AGRADECIMIENTOS

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RESUMEN:

Introducción: La patología cardiovascular es la causa más importante de la mayor tasa de mortalidad que tienen los pacientes con problemas psiquiátricos. En esta tesis se ha revisado la bibliografía sobre la asociación entre los problemas psiquiátricos, y factores de riesgo y patologías cardiovasculares. Se han llevado a cabo estudios observacionales para estimar el riego de eventos cardiovasculares en pacientes con depresión y ansiedad, así como la historia natural de dichas asociaciones y los factores que puedan explicarlas. También se ha estudiado el desarrollo de factores de riesgo cardiovascular en pacientes con problema mentales, los mediadores de dicho desarrollo, y el posible retraso en la detección los factores de riesgo investigados.

Métodos: Esta tesis se presenta por compendio de publicaciones.

En primer lugar se realizó una revisión narrativa de literatura que después se completó con dos revisiones sistemáticas; en la primera se revisaron estudios que presentaran el riesgo de ictus en pacientes con trastornos de ansiedad; la segunda fue de estudios que presentaran estimaciones de riesgo cardiovascular, en pacientes con patología mental severa. En ambas revisiones se hicieron búsquedas en bases de datos y búsquedas manuales. Los artículos se seleccionaron según criterios predefinidos, se valoró su calidad y se incluyeron en un meta-análisis.

Posteriormente se llevaron a cabo dos estudios prospectivos empleando una base de datos clínicos de atención primaria.

Los estudios contenidos en esta tesis no presentaron ningún problema ético. Todos ellos se llevaron a cabo buscando la excelencia propuesta en el marco de la ética de la virtud, cuya conceptualización está desarrollada en uno de los artículos que presento.

Resultados La revisión bibliográfica mostro una asociación entre algunas patologías psiquiátricas, y factores de riesgo y problemas cardiovasculares. La primera revisión

sistemática mostró que los pacientes con ansiedad tienen un ictus, incrementado en un 24%.

La segunda revisión sistemática mostró que los pacientes con patología mental severa no tienen un riesgo cardiovascular estimado a largo plazo distinto al de las personas sin problemas mentales.

Los estudios prospectivos mostraron que los pacientes con ansiedad o depresión tienen un riesgo amentado de tener un evento cardiovascular. Los factores de riesgo cardiovascular, la medicación antidepresiva y el bajo nivel socioeconómico explicarían en parte esta asociación. También se observó que las personas que tienen depresión o ansiedad tienen eventos cardiovasculares a una edad más temprana.

Los pacientes con depresión ansiedad, esquizofrenia, enfermedad bipolar, y trastornos de personalidad mostraron un riesgo aumentado de desarrollar factores de riesgo cardiovascular. Dicho desarrollo no lo explica completamente la medicación antidepresiva, antipsicótica, ni el nivel socioeconómico de estos pacientes. Los factores de riesgo cardiovascular se detectan a una edad más tardía en pacientes psiquiátricos.

Conclusiones: Existe una asociación entre la patología mental, y los factores de riesgo y eventos cardiovasculares.

La evidencia disponible es suficiente como para recomendar a los clínicos que se debe buscar un control estricto de factores de riesgo cardiovascular en pacientes con problemas mentales.

La investigación en el futuro debería presentar una evidencia cuantitativa y cualitativa más fuerte y detallada sobre la asociación entre la patología mental y cardiovascular. Dicha evidencia debería permitir el desarrollo de intervenciones eficaces y costo efectivas para reducir la incidencia de problemas cardiovasculares en pacientes con problemas psiquiátricos.

SUMMARY:

Introduction: Cardiovascular diseases are the biggest contributor to the higher mortality of patients with psychiatric disorders. In this thesis, the literature on the association between psychiatric disorders, and cardiovascular risk factors and cardiovascular diseases, has been reviewed. Observational studies have been conducted to estimate the risk of cardiovascular events in patients with depression and anxiety. The natural history and the explanatory factors for the associations between depression, anxiety and cardiovascular events, has also been investigated. Finally, I have studied the development of cardiovascular risk factors in patients with psychiatric disorders, the explanatory factors for it, and the possible delay in the detection of these risk factors in psychiatric patients.

Methods: This thesis is presented by portfolio of publications.

First, a narrative review of the literature was carried out, which was then completed with two systematic reviews. The first systematic review approached the risk of stroke in patients with anxiety disorders. The second one reviewed studies that presented estimates of cardiovascular risk in patients with severe mental illness. In both reviews, I conducted electronic and manual searches. The articles were selected, and assessed for quality, according to predefined criteria, and included in a meta-analysis.

Subsequently, two prospective studies were carried out using a primary care data.

The studies contained in this thesis raised no ethical dilemas. All of them were carried out seeking the excellence proposed in the virtue ethics framework, which conceptualization is developed in one of the articles I present.

Results The literature review showed an association between some psychiatric disorders, and cardiovascular risk factors or cardiovascular diseases. The first systematic review showed that patients with anxiety have a risk of stroke increased by 24%. The second

systematic review showed that patients with severe mental illness do not have a higher estimated long-term cardiovascular risk compared to those without mental disorders.

The prospective studies showed that patients with anxiety or depression have an increased risk of having a cardiovascular event. Cardiovascular risk factors, antidepressant medication, and low socioeconomic status, partly explain these associations. It was also observed that patients with depression or anxiety have cardiovascular events at an earlier age.

Patients with depression, anxiety, schizophrenia, bipolar, or personality disorders showed an increased risk of developing cardiovascular risk factors. This was not fully explained by antidepressant or antipsychotic medication, or by socioeconomic status. Cardiovascular risk factors are detected at an older age in psychiatric patients.

Conclusions: There is an association between mental disorders and cardiovascular risk factors, and cardiovascular events.

The available evidence is sufficient to recommend that clinicians aim for a strict control of cardiovascular risk factors in patients with mental disorders.

Future research should present stronger and more detailed quantitative and qualitative evidence on the association between mental and cardiovascular diseases. Such evidence should help to develop effective and cost-effective interventions to reduce the incidence of cardiovascular diseases in patients with psychiatric problems.

ÍNIDICE DE ABREVIATURAS

IAM: Infarto Agudo de Miocardio

CI: Cardiopatía Isquémica

ECV: Enfermedad Cardiovascular

HTA: Hipertensión Arterial

DM: Diabetes Mellitus

FORMATO EMPLEADO EN ESTA TESIS

Antes de la elaboración de la tesis valoré detenidamente, junto con mis directores, las ventajas e inconvenientes de presentar este trabajo como un compendio de publicaciones o como una tesis tradicional. Finalmente, tanto mis directores como yo, estimamos que el formato más adecuado teniendo en cuenta la metodología del trabajo era una tesis por compendio de publicaciones.

Esta tesis incluye por tanto los artículos que se presentan a continuación. Todos ellos fueron concebidos en el orden en que son presentados, a excepción del artículo sobre el planteamiento ético de los estudios que fue escrito en distintos momentos a lo largo del tiempo transcurrido en la realización del trabajo.

Artículos incluidos en esta tesis:

I. Pérez-Piñar M, González E, Ayerbe L. ¿Tesis doctoral tradicional o por compendio de publicaciones? *Semergen*. 2016 Mar 26. pii: S1138-3593(16)00081-2. (Cite Score 2015: 0.19)

II. Pérez-Piñar M, Ayerbe L. Virtue ethics of clinical research. *Perspectives in Clinical Research*. 2017 8(2):103-4 (Cite Score 2015: 1.20)

III. Pérez-Piñar M, Ayerbe L, González E, Mathur R, Foguet Q, Ayis S. Anxiety disorders and risk of stroke; a systematic review and metanalysis. *European Psychiatry*. 2017 Jan 27;41:102-108. (Cite Score 2015: 3.75)

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VI. Pérez-Piñar M, Mathur R, Foguet Q, Ayis S, Robson J, Ayerbe L. Cardiovascular risk factors among patients with schizophrenia, bipolar, depressive, anxiety, and personality disorders. *European Psychiatry* 2016; (35):8-15 (Cite Score 2015: 3.75)

Las consideraciones sobre el formato de la tesis requirieron algunas búsquedas bibliográficas, así como consultas a investigadores experimentados, y no tardamos mucho en observar la relevancia del tema. El resultado de esta pequeña investigación preliminar adquirió por tanto un valor académico propio, ha sido publicado en *SEMERGEN Medicina de Familia*, y constituye el primero de los artículos que presento.[1]

¿Tesis doctoral tradicional o por compendio de publicaciones?

Traditional doctorate thesis or by a compendium of publications?

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Conflicto de intereses: ninguno

Palabras clave: Investigación biomédica, Facultad de medicina, Publicación, Trabajo académico, Tesis, Estudios de doctorado.

El aumento del número de estudios de investigación y tesis doctorales escritas, supervisadas, o evaluadas por médicos de atención primaria es una de las consecuencias positivas de la creciente presencia de la medicina familiar en las universidades.[1] Las tesis doctorales se han considerado siempre como una modalidad de "literatura gris" y por ello de difusión muy limitada a pesar de los hallazgos que contengan.[2] Por ello se han establecido normas en las diferentes facultades de medicina que contemplan la posibilidad u obligatoriedad de publicar el contenido de la tesis, en parte o en su totalidad, antes de su defensa, y en muchas universidades se acepta la presentación de Tesis por Compendio de Publicaciones (TCP).[3, 4] En este artículo presentamos ventajas e inconvenientes de la tesis tradicional (TT), el texto que presenta los resultados de un trabajo de doctorado, y es redactado específicamente con ese propósito, frente a la TCP, para su consideración tanto al escribir una tesis como al evaluarla.

La TT representa una base de conocimientos, sobre los que el doctorando puede elaborar futuros artículos, pero sin impacto directo sobre la comunidad científica.[2] En cambio, la TCP tiene, ya en el momento de presentarse un valor clínico y científico, reconocidos por editores y revisores externos.[4] Además, al sumar al currículo no solo el doctorado sino también publicaciones, las TCP mejoran las oportunidades de carrera del doctorando y de sus coautores.[3, 4]

Los médicos que abordan la redacción de una TT cuentan con la ventaja de que estas no suelen tener límite de palabras, permitiendo una exploración profunda y amplia de todas las implicaciones de la pregunta, los métodos, y los resultados. Además a una TT se le puede dar un formato muy perfilado, y obtener una gran coherencia entre los capítulos y las ideas que se proponen. En cambio, los artículos de una TCP se ciñen al límite de palabras que exigen los editores de las revistas. Esto obliga al doctorando a condensar y sintetizar el material relevante, lo cual no deja de ser una competencia muy necesaria a alcanzar por el

doctorando. Además, en las TCPs la aportación de editores y revisores, y la necesidad de que cada artículo tenga valor de modo independiente, puede llevar a la repetición de argumentos, y a que la tesis no tenga un eje lineal y presente ideas conectadas a veces de modo indirecto.[3] No obstante este formato da al doctorando la oportunidad de reflejar el debate científico en el que ha participado, donde siempre hay ideas que se plantean, se debaten, se revisan, y se confirman o se descartan en un ámbito multidisciplinario. En todo caso una TCP suele presentarse con un texto que introduce y enlaza las diferentes publicaciones, clarifica la aparente desconexión que pueda haber entre ellas, y permite presentar ideas relevantes que los editores hayan dejado sin publicar.[3] Por ultimo, durante la presentación de la TCP el tribunal puede exigir al doctorando la explicación de algún argumento que crean que está expuesto de modo demasiado breve o con escasa profundidad.

Otra ventaja de las TT es que representan mejor el trabajo realizado exclusivamente por el doctorando, si bien el texto recibe durante su realización aportaciones de directores y colegas. A cambio, no se puede decir en muchos casos que la TCP sea obra exclusiva del doctorando al estar la mayor parte de los artículos escritos por un número de autores. Sin embargo habitualmente los primeros autores hacen la contribución más significativa al artículo, de modo que se puede asumir que el doctorando ha hecho el mayor esfuerzo en el trabajo que firma como primer autor. Además en una TCP debe apreciarse positivamente el trabajo realizado por el doctorando para coordinar a los coautores, una capacidad enormemente valiosa en un investigador.

El médico de familia que aborde la elaboración de una tesis debe decidir, en colaboración con sus directores, que formato es el más apropiado teniendo en cuenta, las normas de la universidad, las ventajas de cada uno, el contenido de la tesis, la metodología a emplear, y las circunstancias personales y profesionales de las personas implicadas en el proyecto.[3]

English version:

The increase in the number of research studies and doctoral theses written, supervised, or evaluated by primary care physicians is one of the positive consequences of the growing presence of family medicine in universities.[1] Doctoral theses have always been considered as a type of "grey literature" and therefore of very limited impact, regardeless of the findings that they may have.[2] Therefore, the different medical schools have stablished new rules that contemplate the possibility or the obligation to publish part or all the thesis, before it is presented; in many universities the presentation of a Thesis by Compendium of Publications (TCP) is accepted.[3, 4] In this article we discuss the advantages and disadvantages of the traditional thesis (TT), the text that presents the results of a doctoral work, and is written specifically for that purpose, against the TCP, for consideration when writing or evaluating a thesis.

The TT represents a base of knowledge, from which the PhD student can elaborate future articles, but without direct impact on the scientific community.[2] In contrast, a TCP has, at the moment of being presented, clinical and scientific value, recognized by editors and external reviewers.[4] Furhtermore, by adding to the curriculum not only the PhD but also the publications, the TCP improves the career opportunities of the PhD student and his/her co-authors.[3, 4]

Doctors who write a TT have the advantage of not having a word limit, which allows for a deep and comprehensive exploration of all the implications of the question, methods, and results. In addition a TT can be given a very defined format, reporting very coherently the consistency between the chapters and the ideas that are proposed. However, the articles of a TCP are constrained by the word limit required by the editors of the journals. This forces the PhD student to condense and synthesize the relevant material, which is noetheless a very necessary skill to be aquired by the doctor. Morevover, in the TCPs the contribution of

editors and reviewers, and the need for each article to have independent value, can lead to the repetition of arguments, a thesis without a clear structure, and the presentation of ideas connected sometimes indirectly.[3] Nevertheless, this format gives the PhD student the opportunity to reflect the scientific debate in which he / she has participated, where there are always ideas that are raised, debated, reviewed, and confirmed or discarded in a multidisciplinary area of knowledge. In any case, a TCP is usually presented with a text that introduces and links the different publications, clarifies the apparent disconnection between them, and allows to present relevant ideas that the editors may have left unpublished.[3]

Finally, during the presentation of the TCP the examiners may require the PhD student to explain some arguments that they may find have been reported too briefly.

Another advantage of TTs is that they represent the work conducted almost exclusively by the PhD student, even though the text always receives contributions from supervisors and colleagues. In return, it can not be said in many cases that TCP is the work of the PhD student exclusively, since most of the articles are written by a number of authors. However, normally the first author makes the most significant contribution to the article, so it can be assumed that the PhD student has made the greatest effort in the work that he/she signs as first author. Also in a TCP, the work conducted by the PhD student to coordinate the co-authors, an enormously valuable skill for a researcher, should be appreciated.

The family doctor who approaches the elaboration of a thesis must decide, together with his or her supervisors, which format is the most appropriate taking into account, the rules of the university, the content of the thesis, the methodology to be used, and the personal and professional circumstances of the people involved in the project.[3]

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1. INTRODUCCIÓN

1.1 Relevancia de la patología psiquiátrica en el mundo.

Se estima que un 14,3% de las muertes, y un 7,4% de los años de vida ajustados por discapacidad (AVADs) perdidos en todo el mundo se pueden atribuir a patología psiquiátrica.[2, 3] Los trastornos mentales son por ello la principal causa de años de vida potenciales perdidos (AVPP) a nivel mundial.[2, 3]

Entre la patología psiquiátrica, la depresión es la que tiene un mayor impacto mundial, representando un 40,5% de todos los AVADs perdidos debido a problemas mentales.[3] La depresión es un problema cuyos síntomas incluyen estado de ánimo irritable o bajo, trastornos en el sueño, cambios en el apetito, cansancio, y sentimientos de inutilidad, odio a si mismo, o culpa.[4]

Los trastornos de ansiedad son el segundo grupo de enfermedades psiquiátricas con mayor impacto a nivel mundial. Representan un 14.6% de los AVADs perdidos atribuibles a problemas de salud mental.[5] Los trastornos de ansiedad se caracterizan por la presencia de un sentimiento de anticipación o preocupación incapacitante, persistente e incontrolable. La ansiedad están comúnmente asociada con la depresión, el abuso de alcohol u otras sustancias, y problemas de salud física.[6]

La esquizofrenia representa el 7.4% de todos los AVADs perdidos en el mundo atribuibles a problemas psiquiátricos.[5] La esquizofrenia es un síndrome conductual y cognitivo complejo y heterogéneo. Su presentación clínica incluye síntomas positivos, como los delirios y alucinaciones, y síntomas negativos como la baja motivación, el deterioro cognitivo, la reducción del habla y la retirad social.[7]

Los trastornos bipolares representan un 7% de los AVADs perdidos en el mundo atribuibles a problemas psiquiátricos.[5] Estos trastornos son un problema crónico y recurrente, caracterizado por fluctuaciones del estado de ánimos y los niveles de energía. Los pacientes

experimentan fases de depresión, y fases de manía durante las cuales tienen un estado de ánimo anormalmente alto y un aumento excesivo de la actividad motora.[8]

Los trastornos de personalidad afectan a un 4-12% de la población adulta.[9] Las personas con trastorno de personalidad presentan anomalías persistentes y generalizadas en las relaciones sociales. Estos pacientes parecen tener un modo de percibir, relacionarse y pensar en el mundo exterior, y en si mismos, inflexible, que se desvía además marcadamente de las expectativas culturales. Las personas con trastorno de la personalidad tienen un rango más limitado de emociones, actitudes y comportamientos con los que hacer frente a las tensiones de la vida cotidiana.[9]

1.2 La salud cardiovascular de los pacientes con patología psiquiátrica

Los pacientes con problemas psiquiátricos tienen una expectativa de vida acortada. Viven entre 1.4 y 32 años menos que las personas sin patología mental.[2, 10, 11] Sin embargo, la causa directa más frecuente de estas muertes prematuras no son los trastornos mentales sino las enfermedades físicas, siendo la patología cardiovascular la principal responsable de esta mortalidad aumentada.[10, 11]

Parte de la atención sanitaria a personas tributarias de asistencia psiquiátrica es labor del médico de familia. En muchas otras ocasiones, sobre todo cuando presentan síntomas agudos, o problemas más complejos, se atiende a estos pacientes en los servicios de psiquiatría. Aunque la contribución de los psiquiatras a la prevención de patología cardiovascular en estos pacientes se ha debatido, parece que esta labor encaja fundamentalmente con las funciones de la medicina de familia. De acuerdo a los principios que la originaron, la atención primaria representa el primer nivel de contacto de los individuos, la familia, y la comunidad con el sistema de salud, lleva lo más cerca posible la atención de salud al lugar donde residen y trabajan las personas, y constituye el primer

elemento de un proceso permanente de asistencia sanitaria. La atención primaria incluye entre sus funciones más importantes la prevención de patologías comunes y promoción de la salud.[12]

En los últimos años ha habido intentos en atención primaria de mejorar la salud física, en concreto la salud cardiovascular, de los pacientes psiquiátricos.[13] Sin embargo hay varios factores que dificultan esta labor. Muchos de los síntomas que tienen los pacientes con problemas psiquiátricos, como el deterioro cognitivo o la baja motivación, conducen a un abandono del cuidado de su salud física y a estilos de vida poco saludables. Algunos de estos pacientes tienen problemas para usar el sistema sanitario. Al estar este organizado en niveles asistenciales bastante estancos, puede prestar una atención en muchos casos poco personalizada. Asimismo, es necesario un alto grado de cooperación del paciente que tiene por ejemplo que solicitar, recordar, y acudir a citas en varios centros distintos. Además, muchos clínicos no están suficientemente preparados y mentalizados para atender a estos pacientes e identifican en ellos como comportamientos inaceptables sus modos de proceder en ocasiones extraños, que no otra cosa que los signos de la patología psiquiátrica. A veces estos enfermos pueden ser agresivos o bruscos en el trato, lo cual intimida a médicos y enfermeras y deteriora la calidad de la atención sanitaria. También es posible que los clínicos subestimen la capacidad de los pacientes con patología psiquiátrica para entender y seguir sus instrucciones y consejos.[11]

Por otro lado, muchas de las intervenciones que se han planteado para mejorar la salud cardiovascular de los pacientes con problemas psiquiátricos, e intentar igualar su riesgo cardiovascular al de las personas sin problemas mentales, se encuentran con una evidencia epidemiológica pobre, y consiguen unos resultados muy escasos.[11, 14] La distribución de los problemas cardiovasculares entre los pacientes psiquiátricos es un hecho insuficientemente

estudiado y ello impide el desarrollo de intervenciones eficaces que puedan reducir su riesgo cardiovascular al nivel de la población general.

En esta tesis, en primer lugar se revisara la bibliografía existente sobre la asociación entre los distintos problemas psiquiátricos y las diferentes patologías y factores de riesgo cardiovascular. Posteriormente, de acuerdo a los resultados de dicha revisión se plantearan las hipótesis que se investigaran en los trabajos originales que se presentan.

2. CONSIDERACIÓN ÉTICA DE LOS ESTUDIOS CONTENIDOS EN ESTA TESIS

El escrito presentado con el formato de la tesis, igual que las revisiones sistemáticas presentados en el capítulo tres, no requirieron valoración previa por ningún comité de ética. Los artículos de investigación sobre factores de riesgo y eventos cardiovasculares, presentados en los capítulos cuatro y cinco, se realizaron empleando datos de atención primaria anonimizados. Tal y como se menciona en dichos artículos, la consideración ética del uso de dicha información para investigación fue establecida por la los directivos del *National Health Service* británico en el momento de desarrollar los programas informáticos que ponen los datos clínicos a disposición de los investigadores. Por este motivo tampoco fue necesaria la aprobación de un comité de ética para la realización de estos estudios.

Sin embargo existe una naturaleza ética en todas las decisiones que tomamos como clínicos e investigadores.[15, 16] La *Ética de Principios*, que es la empleada por los comités de ética, es un instrumento eficaz al plantear unos mínimos morales que el médico e investigador deben respetar.[15] Dichos comités suelen observar con gran sensibilidad el mal que se debe evitar, por ejemplo el uso de información confidencial sin permiso o el riesgo al que sometemos a los participantes en un estudio de investigación.[16, 17] No obstante la ética de principios impone un compromiso personal mínimo, ya que apenas considera el bien que debemos perseguir en el ejercicio de nuestra actividad clínica e investigadora. Lo que en las últimas décadas se ha llamado *Ética Clínica de la Virtud* centra su atención, observa, estudia, y debate sobre el bien que nuestro trabajo tiene por objetivo.[15, 16] Dicho planteamiento, observa los máximos éticos a los que nuestra actividad debe aspirar, rescata conceptos elaborados por filósofos clásicos[18, 19] y complementa muy bien a la ética de principios. Si bien la ética de la virtud puede mejorar nuestra actividad clínica e investigadora, su aplicación requiere una mayor elaboración intelectual.

Al mismo tiempo que realizaba, y en íntima relación con ellas, mis investigaciones clínicas y epidemiológicas, he escrito un artículo con el que espero haber contribuido al desarrollo conceptual de la ética de la virtud. En el abordo sus ventajas y limitaciones, sus bases teóricas, su finalidad, y su relación con los motivos más profundos que nos hacen ser médicos e investigadores. Dichas reflexiones han estado presentes en todos los estudios presentados en esta tesis. Por esto he considerado que, igual que algunos trabajos de investigación incluyen descripciones elaboradas de la metodología empleada, el artículo sobre la ética médica de la virtud debía formar parte de la tesis. De este modo espero dejar también patente mi capacidad para realizar un trabajo multidisciplinario que entiendo es lo que se exige a un medio de familia y a un candidato a doctor.

El artículo en el que elaboro el marco de la ética de la virtud en investigación clínica ha sido publicado en *Perspectives in Clinical Research* y es presentado a continuación.[20]

Virtue ethics of clinical research

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Key words: Research ethics, virtues, clinical research, biomedical research

A widely accepted idea of clinical science is that it seeks the truth, and that the knowledge acquired should be of benefit to patients.[1] Therefore, as clinical researchers we give response to two concerns deeply rooted in the human nature: the desire to know, and the need to help someone suffering.[2, 3] However, the ideas and values that sustain clinical research, and take it to its most genuine objectives, are subject to numerous tensions. For centuries medicine has been gradually departing from its anthropocentric origin to become a political, social, and economic instrument.[3] It is difficult for researchers based in clinical settings to remain focused on human good when the clinical activity is distracted from it by so many issues. Currently the lack of ethical references widely accepted by the scientific community makes the concepts of good, human life, or human health uncertain; we have been left with a reduced number of hesitant principles against the powerful forces of market and ideology.[3] Sometimes, the personal circumstances of the researcher, including the pressure to publish or attract income, increase the constraints imposed on research even more.[3, 4] All these issues can blur the values that sustain research, undermine the objectivity, accuracy, and reliability of our studies, and can make the researcher adopt the role of a businessman or a bureaucrat, who conducts a type of research that is empty of its meaning. A thorough exploration of the ends of our work and its ethical nature can help rediscover the values and ideas that should structure clinical research and lead to a scientific production of the highest quality. Ethics in the context of clinical research is nowadays dominated by principles and regulations,[5] which provide a manageable, sometimes simplistic, idea of the good, and demand very little personal engagement from the researcher.[3]

Virtue ethics is rooted in classical philosophy and fills many of the gaps on the intellectual framework in which research is currently conducted.[2, 3, 6] Virtue ethics acknowledges that there is an ethical nature in all activities related to research (not only in ethical dilemmas), including the conceptualisation of the studies, the distribution of work, and the way we treat

the members of our team. Virtue ethics also revives the idea that all of us are naturally inclined to move towards what we perceive as good.[6] Virtues are the intellectual and moral qualities that we can acquire to define correctly, and move effectively towards, that ethical horizon; the qualities that take us to our natural ends, ultimately the qualities that make us good.[2, 6] Ethics, based on virtues, is flexible as there are no pre-established solutions for specific questions and the researcher has to deliberate the best way to look for the good in each specific circumstances. The ethical character of the researcher is thereby the ultimate guarantor of ethical excellence and we cannot deflect our responsibility on a committee or the government. Virtue and principle ethics complement, balance, and enrich each other. There are two main points that require practical action from the perspective of virtue ethics: the acquisition of the virtues needed to conduct scientific studies of the highest quality, and the provision of a research community where these virtues can be constantly improved.[3] We cannot do any good to our patients if the evidence we report in our studies is weak. Ethical excellence therefore encompasses scientific excellence, which includes virtues such as being knowledgeable of the clinical principles and research methods, the capability to think critically, being open-minded, creative, disciplined, diligent, and focused.[7] However, the researcher who aims for ethical excellence must also work on virtues that go beyond the technical characteristics of a good scientist, for example, honesty, compassion, and some degree of self-effacement that allows to move not only for our own good.[1] The virtue of prudence is the one that articulates the other virtues, and closes the gap between cognition of the good and motivation to do the good. We learn about virtue mostly from the example of a virtuous colleague and we acquire virtues through hard work and practice.[3, 6]

However, unless virtue ethics is based on a firm idea of the good, it becomes relativist and meaningless. Aiming to define the good that should motivate our research makes us face a number of fundamental questions including: what is a human being; where is human dignity

based; and is there an ethical order transcending the human being? Modern man sometimes feels uncomfortable reflecting on, or discussing, these issues but patients are very rarely sceptical about their own suffering, and expect us to search for answers to all these questions. The current climate of moral scepticism, and moral atomism, is therefore unjustified.

The concept of the good, together with the realities of disease, suffering, and death are complex and their understanding demands reflection and discussion on a diversity of ideas. Many scientists believe that things that cannot be verified experimentally do not deserve acknowledgement. These would include all ethical reflections. It seems clear to us that searching for the good and becoming a virtuous researcher requires an intellectual approach that goes beyond the traditional scientific methodology.

In conclusion, given the proximity of clinical research to the reality of disease, concurring an adequate training and the necessary material means, the power of the clinical researcher to do good to different patients seems enormous. The moral imperative imposed by this fact goes beyond many political, economic and social circumstances. Being a researcher is a privilege, hence ignoring our ethical commitment would be ungrateful. Ultimately, it would also be disloyal to the universal vocation to search and do the good. Our commitment as clinical researchers requires that we look for ethical excellence throughout our professional activity. A continued reflection, self-examination, and dialogue with colleagues and society are required to understand the ethical nature of clinical research. Searching for the good in all steps of our practice gives clinical research its full meaning and researchers their maximum fulfilment.

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3. REVISIÓN BIBLIOGRÁFICA

En este capítulo se presentan los resultados de diferentes búsquedas bibliográficas que abordan preguntas específicas sobre la epidemiología de los factores de riesgo y eventos cardiovasculares en el contexto de la enfermedad psiquiátrica. El objetivo de este capítulo es por tanto definir con la mayor exactitud posible hasta donde llega el conocimiento disponible en este campo, y donde se encuentran las áreas concretas que deben ser abordadas por futuras investigaciones, para aportar una evidencia epidemiológica fuerte, que permita mejorar los resultados clínicos en pacientes con patológica psiquiátrica.

En primer lugar se buscaron revisiones sistemáticas, ya que están consideradas como los trabajos que aportan una evidencia de más nivel.[21] Se comprobó que en algunos casos no había investigaciones llevadas a cabo con esta metodología, por lo que se revisaron también estudios independientes.

3.1 La patología cardiovascular en pacientes con trastornos psiquiátricos

Los resultados de las búsquedas bibliográficas realizadas mostraron un gran número de revisiones sistemáticas, que reflejan el riesgo de distintos eventos cardiovasculares en pacientes con diferentes problemas psiquiátricos.

Cinco revisiones sistemáticas, publicadas entre 1999 y 2016, pusieron de manifiesto un riesgo aumentado de enfermedad coronaria en pacientes con depresión. [22-26] De igual manera, dos trabajos recientes, los meta-análisis publicados en 2011 y 2012, mostraron una asociación entre la depresión y el riesgo de ictus.[27, 28] En uno de ellos se observó además una mayor mortalidad en los pacientes con depresión que sufren ictus.[27]

Otro meta-análisis publicado en 2010 informó de un riesgo incrementado de sufrir enfermedad coronaria en pacientes con ansiedad.[29] Por otro lado una revisión sistemática de

2015 mostró un riesgo de enfermedades coronarias aumentado específicamente entre los pacientes con trastorno de pánico.[30]

Un meta-análisis publicado en 2013 observó un aumento de la incidencia de enfermedad coronaria entre los pacientes esquizofrénicos, pero sin valor estadísticamente significativo.[31] Sin embargo, dos meta-análisis, publicados en 2013 y 2014 mostraron la asociación de la esquizofrenia con una mayor incidencia de ictus.[31, 32] En uno de ellos se observó además una mayor mortalidad entre los pacientes esquizofrénicos que sufren un ictus.[32]

Una revisión sistemática publicada de 2014 mostró un riesgo aumentado de ictus entre los pacientes con enfermedad bipolar.[33] Sin embargo la misma revisión mostró que el riesgo de enfermedad coronaria en estos pacientes no estaba aumentado de modo estadísticamente significativo.

La patología cardiovascular en pacientes con trastornos de personalidad ha recibido mucha menos atención. No se encontraron revisiones sistemáticas que incluyeran trabajos originales que observaran el riesgo de eventos cardiovasculares en estos pacientes. Un estudio publicado en 2007 observó una asociación entre trastornos de personalidad y un aumento de casos de enfermedad coronaria.[34]

Las tablas 3.1.1, 3.1.2, 3.1.3 y 3.1.4 presentan los resultados encontrados en las revisiones sistemáticas que estudiaron el riesgo de enfermedades coronarias e ictus en pacientes con diferentes enfermedades psiquiátricas.

	Resultados (N studios)	Riesgo. Promedio ponderado	Países	N	Seguimiento (años)	Sugerencias para investigación futura
Wu 2016	IAM (9) CI fatal (8)	1.31(1.09-1.57) 1.36(1.14-1.63)	EEUU Alemania Finlandia Holanda Noruega Reino Unido Suecia China	1190-63469	4-37	Mecanismos de la asociación. Relevancia de los factores de riesgo cardiovascular y de los antidepresivos
Gan 2014	CI (30) IAM (12)	1.30(1.22-1.40) 1.30(1.18-1.44)	Canadá EEUU China Taiwán	660 - 345949	2-37	El efecto de la severidad de la depresión y los mecanismos de su asociación con la CI.
Dong 2012	Ictus (17)	1.34(1.17-1.54)	EEUU Finlandia Holanda Italia Reino Unido Japón	494 - 93676	3-29	Mecanismos de la asociación y si la asociación es distinta para subtipos de ictus.
Pan 2011	Ictus (28) Ictus fatal (8) Ictus no fatal(3) Ictus isquémico (6) Ictus Hemorrágico(2)	1.45(1.29-1.63) 1.55(1.25-1.93) 1.21(0.91-1.62) 1.25(1.11-1.40) 1.16(0.80-1.70)	EEUU Australia Alemania Holanda Reino Unido Japón Taiwán	401-93676	2-29	Los mecanismos de la asociación
Van der Kooy 2007	IAM(8) CI (16) Ictus (10) ECV(7)	1.60(1.34-1.92) 1.48(1.29-1.69) 1.43(1.17-1.75) 1.63(1.26-2.12)	EEUU Dinamarca Finlandia Holanda Reino Unido Japón	500 - 12866	3-37	Los mecanismos de la asociación
Nicholson 2006	CI(21) CI fatal (9)	1.81(1.53-2.15) 1.69(1.34-2.14)	-	124 - 509	4- 21	

Tabla 3.1.1 Revisiones sistemáticas sobre riesgo de eventos cardiovasculares en pacientes con depresión.IAM: infarto agudo de miocardio. CI: Cardiopatía isquémica. ECV: Enfermedad Cardiovascular

	Resultados (N estudios)	**Riesgo. Promedio ponderado**	**Países**	**N**	**Seguimiento (años)**	**Sugerencias para investigación futura**
Roest 2010	CI (20)	1.26(1.15-1.38)	EEUU Holanda Noruega Reino Unido Rusia Suecia Japón	433 - 72359	2-21	Los mecanismos de las asociaciones, cada uno de los resultados y si el tratamiento de la ansiedad afecta a la incidencia de CI
	CI fatal (9)	1.48(1.14-1.92)				
	IAM no fatal (5)	1.43(0.85-2.40)				

Tabla 3.1.2 Revisión sistemática sobre riesgo de eventos cardiovasculares en pacientes con ansiedad .IAM: Infarto agudo de miocardio. CI: Cardiopatía isquémica. ECV: Enfermedad Cardiovascular

	Resultados (N studios)	**Riesgo. Promedio ponderado**	**Países**	**N**	**Seguimiento (años)**	**Sugerencias para investigación futura**
Li 2014	Ictus (6)	1.50(1.25–1.80)	Canadá EEUU Finlandia Suecia China	11580 - 6097834	2-35	Los mecanismos de la asociación, la relevancia de los factores de riesgo cardiovascular, la atención sanitaria y la historia natural de la esquizofrenia
	Ictus fatal (3)	1.65(1.31–2.08)				
Fan 2013	ECV (4)	1.53(1.27- 1.86)	Australia Canadá China Finlandia Taiwán Reino Unido EEUU	2266 - 2310391	1-36	Los mecanismos de la asociación. La relevancia de los factores de riesgo cardiovascular
	CI (9)	1.20(0.93–1.53)				
	Ictus (6)	1.71(1.19-2.46)				
	CHF (5)	1.81(1.42- 2.29)				

Tabla 3.1.3 Revisiones sistemáticas sobre riesgo de eventos cardiovasculares en pacientes con esquizofrenia CI: Cardiopatía isquémica. ECV: Enfermedad Cardiovascular

	Resultados (N studios)	**Riesgo. Promedio ponderado**	**Países**	**N**	**Seguimiento (años)**	**Sugerencias para investigación futura**
Prieto 2014	Ictus (3)	1.74(1.29–2.35)	Dinamarca Suecia Taiwán EEUU	N:13 115 911	6-20	Mecanismos de la asociación
	IAM (4)	1.09(0.96-1.24)				

Tabla 3.1.4 Revisión sistemática sobre riesgo de eventos cardiovasculares en pacientes con enfermedad bipolar. CI: Cardiopatía isquémica. ECV: Enfermedad Cardiovascular

En resumen, existe un gran número de revisiones sistemáticas, que reflejan el riesgo de distintos eventos cardiovasculares en pacientes con diferentes problemas psiquiátricos. La patología mental más estudiada es la depresión, seguida de la esquizofrenia. La evidencia es más escasa para los trastornos de ansiedad y la enfermedad bipolar, y llamativamente pobre para pacientes con trastornos de personalidad.

Como se ha mencionado anteriormente el riesgo de enfermedades coronarias en pacientes con trastornos de ansiedad se ha estudiado en una revisión sistematica.[29] Sin embargo no se encontraron revisiones que abordaran el riesgo de ictus en estos pacientes. Los trastornos de ansiedad son las enfermedades psiquiátricas con mayor frecuencia, y las segundas en impacto, a nivel mundial.[5, 35, 36] Además, lo que es especialmente relevante para esta tesis, son un grupo de trastornos que se maneja en la mayoría de los casos íntegramente en atención primaria.[37] La asociación entre la ansiedad y el riesgo de ictus solo ha sido presentado en artículos independientes, que además muestran resultados contradictorios.[38-41] Para cubrir esta área de evidencia pobre, que se identificó en las búsquedas bibliográficas, se decidió llevar a cabo una revisión sistemática sobre el riesgo de ictus en pacientes con trastornos de ansiedad. Esta revisión sistemática fue expuesta como presentación oral en el congreso regional del este de Inglaterra de la *Society of Academic Primary Care* celebrado en Cambridge (Reino Unido) el 29 de enero 2016. La versión final del trabajo, que presento a continuación ha sido publicada en *European Psychiatry*.[42]

Anxiety disorders and risk of stroke: a systematic review and meta-analysis

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Abstract

Background: Anxiety disorders are the most common mental health problem worldwide. However, the evidence on the association between anxiety disorders and risk of stroke is limited. This systematic review and meta-analysis presents a critical appraisal and summary of the available evidence on the association between anxiety disorders and risk of stroke.

Methods: Cohort studies reporting risk of stroke among patients with anxiety disorders were searched in PubMed, Embase, PsycINFO, Scopus, and the Web of Science, from database inception to June 2016. The quality of the studies was assessed using standard criteria. A meta-analysis was undertaken to obtain pooled estimates of the risk of stroke among patients with anxiety disorders.

Results: Eight studies, including 950759 patients, from the 11764 references initially identified, were included in this review. A significantly increased risk of stroke for patients with anxiety disorders was observed, with an overall hazard ratio: 1.24 (1.09-1.41) p=0.001 No significant heterogeneity between studies was detected and the funnel plot suggested that publication bias was unlikely. Limited evidence suggests that the risk of stroke is increased shortly after the diagnosis of anxiety and that risk of stroke may be higher for patients with severe anxiety.

Conclusions: Anxiety disorders are a very prevalent modifiable condition associated with risk of stroke increased by 24%. This evidence could inform the development of interventions for the management of anxiety and the prevention of stroke. Further studies on the risk of stroke in patients with anxiety, and the explanatory factors for this association, are required.

Key words: Stroke, Cohort studies, Systematic review, Anxiety disorders

1. Introduction

Anxiety disorders are the most common mental health problem worldwide with lifetime prevalence in the general population, varying across countries, up to 29%.(1-3) It is also the sixth global leading cause of disability, with no discernible change observed from 1990.(4) Stroke is the second most common cause of death, and the third most common cause of reduced disability-adjusted life-years (DALYs), worldwide.(5, 6) Most of the burden of stroke affects low and middle-income countries.(7) Primary prevention of stroke is particularly important because 76% of strokes are first events.(8) Anxiety disorders can have a direct effect on incidence of stroke and also an indirect effect as they may be associated with other cardiovascular risk factors and markers of high cardiovascular risk.(9, 10) While the association between anxiety disorders and coronary artery disease is well established,(11) their impact on the risk of stroke has received less attention. Previous reviews on the associations between anxiety and cardiovascular disease (12-17) do not present specific results for stroke, or do not include the most updated studies. A better understanding of the association between anxiety disorders and stroke would strengthen the evidence for causality and, since anxiety disorders are modifiable conditions, it could also inform the development of clinical and public health interventions for the management of anxiety and the prevention of stroke. This systematic review and meta-analysis presents an up to date critical appraisal and summary of the available evidence on the association between anxiety disorders and risk of incident stroke.

2. Methods

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria were used to undertake this review (Appendix A).(18) Electronic searches were conducted by three

authors (MPP, EG and LA) in PubMed, Embase, PsycINFO, Scopus and the Web of Science, from database inception to the 7th June 2016.

We aimed to identify studies in compliance with the following inclusion criteria:

1) Cohort study design

2) Reporting of original research data

3) Anxiety disorder assessed as exposure

4) Incident strokes reported as outcome

5) Direct reporting of relative risk (RR), odds ratio (OR), or hazard ratio (HR) with corresponding 95% confidence intervals (CIs), or sufficient raw data such that estimates could be calculated.

The search strategy is presented in appendix B. The titles and abstracts of all the references identified in the initial search were checked against inclusion criteria. Papers citing all the included studies, or relevant reviews (12-17) were also searched in the Web of Science and considered for inclusion. The bibliography of all papers fitting the inclusion criteria and relevant reviews (12-17) was checked as well for further articles. There were no restrictions on the basis of language, sample size or duration of follow-up. Studies were excluded if they were:

1) Limited to specific clinical outcomes (e.g. haemorrhagic stroke)

2) Conducted in specific patient sub-populations (e.g. postmenopausal women)

3) Reporting a composite outcome (e.g. stroke and coronary artery disease combined) unless separate results for stroke patients were identified.

4) Cross sectional in design

5) Studies with retrospective recruitment.

Authors of the studies were contacted in some cases, as similarities between articles indicated the possibility of multiple publications from the same cohort. Where several

studies reported results from the same population, data were taken from the publication with the longest follow-up. Data were extracted from the included studies using a predefined template and the quality of each study was assessed using standard criteria (appendix C).(19) A meta-analysis was undertaken to obtain pooled estimates of the risk of stroke among patients with anxiety disorders. A random-effect model was used to summarise the mean estimated effect (hazard ratio), obtained from the included studies and results were graphically presented in a forest plot. The assumption made was that the size of the true effect varies from one study to the other, and that the studies considered in our analysis constitute a random sample of all possible effect sizes that could have been observed. The random-effect approach was considered preferable to the fixed-effect approach where the true effect size in the latter is assumed to be the same in all studies.(20) The heterogeneity between studies was measured using I-squared index that represents the percentage of the total variation which is due to differences between studies. Chi-squared statistic was used to test the significance of the heterogeneity.(21) When participants in the studies had been interviewed about symptoms of anxiety disorders at more than one time point, e.g. in the previous month and in the previous five years, the assessment referring to the time point closest to the date of study entry was included in the analysis as it was considered to be less affected by recall bias. When a study reported results from a multivariable model exploring the association between anxiety and stroke, and then further modeling had been conducted to explore potential explanatory factors for the association, only the results from the first model were included in the meta-analysis. When a study reported risk of stroke at one time point after the diagnosis of anxiety, and after examinations of the HRs for each year of follow up, an estimate of risk of stroke at a different time point had also been calculated, data from the first estimate was included in the meta-analysis. A funnel plot was used to investigate possible publication bias, true heterogeneity and other methodological

irregularities.(22) Sensitivity analyses were performed, first to exclude two studies, which differ in measures of anxiety and age categorization from the rest of the papers,(23, 24) one at a time and simultaneously, and second, to exclude one study with very large variance,(25) to examine the impact of each exclusion on the pooled estimate and on the heterogeneity of the studies included.

3. Results:

The electronic and hand searches identified 11764 references, six of which were reviews relevant to the topic.(12-17) A total of 46 full text studies were assessed for inclusion. Finally, eight studies were considered to comply with inclusion criteria and were included in this review (Figure one).

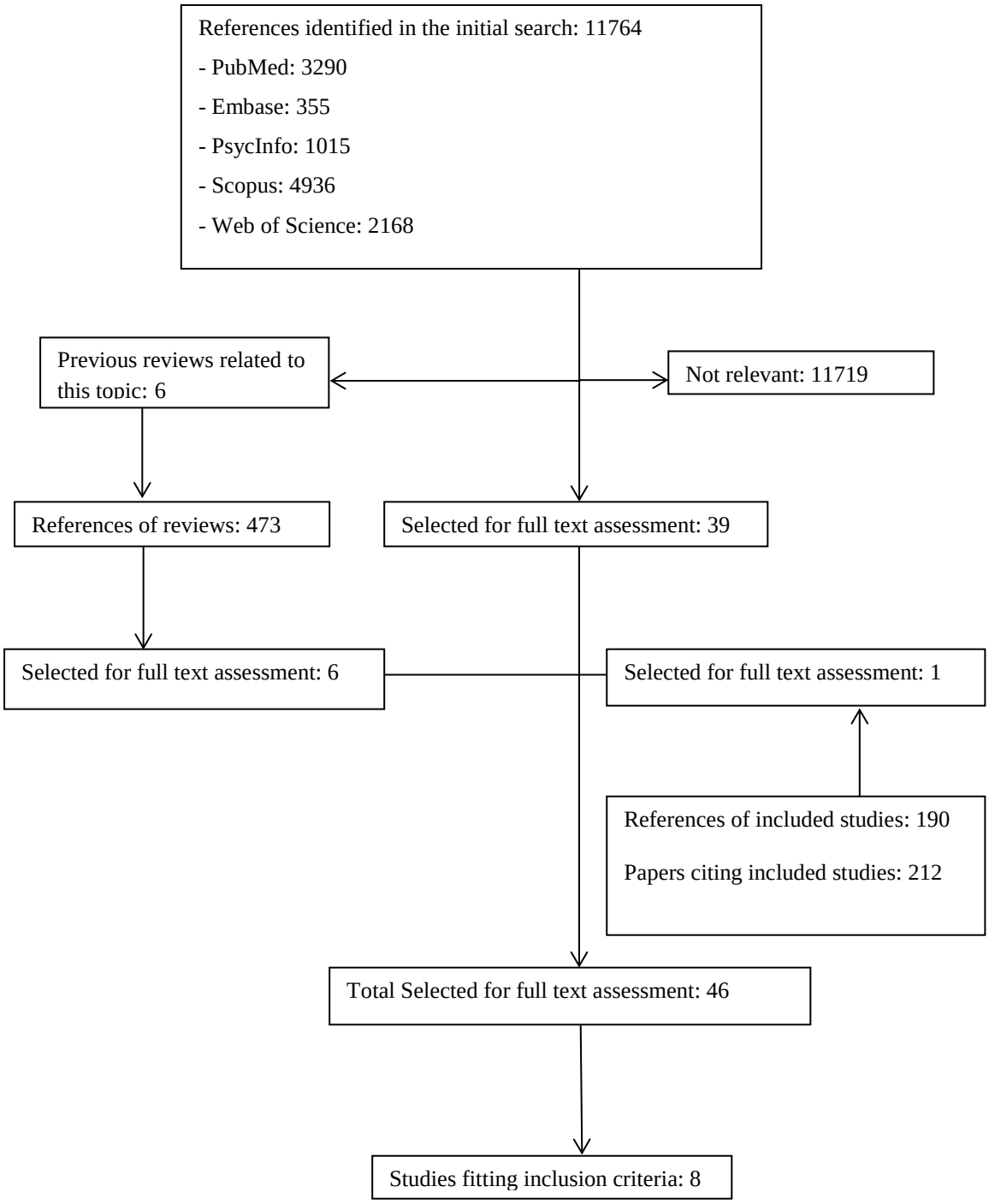

Figure 1. Results of literature search

The characteristics of these studies are presented in table one.

	Vogt 1994	Bowen 2000	Surtees 2008	Chou 2012	Lambiase 2014	Mathur 2015	Portegies 2016	Stewart 2016
Country	USA	Canada	UK	Taiwan	USA	UK	The Netherlands	USA
Data source	Epidemiological	Medical records	Epidemiological	Medical records	Epidemiological	Medical records	Epidemiological	Epidemiological
N	1529	2657	20627	390309	6019	524952	2625	2041
Age	≥18	>15	41 to 80	≥20	25-74	≥20	≥45	≥60
Female %	54	59	57	46	54	47	55	73
Follow-up	15 years	12 years	12 years	10 years	22 years	10 years	20 years	9 years
Anxiety assessment	Bradburn Worries Index	ICD-9 DSM-III DSMIIIR	Health & Life Experience (GAD)[a]	ICD-9 DSM-IV TR (PD) [b]	General Wellbeing scale	Primary care records	Hospital Anxiety Depression scale	Patient Questionnaire
Anxiety N	817	866	NR	1725	1953	22128	343	849
Stroke assessment	ICD-7	ICD-9	ICD-9 ICD-10	ICD-9	ICD-9	Medical records	Medical records	ICD-9 ICD-10
Stroke n (%)	Not reported	44 (1.6)	595 (2.9)	19148 (4.9)	419 (7.0)	987 (0.2)	332 (12.6)	235 (11.5)
Adjustment for covariates	Age, sex, smoking, Health status, SES [c] Duration of health plan membership	Age sex	Age sex CV Risk factors [d] SES [c] Pmh[e]:MI Fh[f] stroke Antidepressant use	Age sex Comorbidities Regular medication	Age sex Ethnic. Education Marital status	Age sex Ethnic.	Age sex	Age sex Ethnic. CV Risk factors [d]
Hazard Ratio (CI)	0.91 (0.63-1.33)	2.00 (1.09-3.64)	0.81 (0.33-1.98)	1.38 (1.12-1.71)	1.43 (1.14-1.80)	1.17 (0.91-1.51)	1.06 (0.76-1.48)	1.20 (0.92-1.56)

Table 1. Characteristics of the studies included in this review. a- GAD: Generalised anxiety disorder, b- PD: Panic disorder, c- SES: Socioeconomic Status, d- CV Risk factors: Blood pressure , cholesterol, diabetes, smoking, obesity. e- PMH: Past medical history, f- FH: Family history

All of them were considered to be of high quality (Appendix C),(19) they were all population based, and included a total of 950759 patients.(23-30) Three studies had been conducted in the USA, two in the UK, one in Canada, one in Taiwan, and another one in The Netherlands. Three of them used medical records,(26, 27, 29) and five included participants from epidemiological surveys.(23-25, 28, 30) Six studies included patients with all types of anxiety disorders, in one study participants were examined specifically for generalised anxiety disorder,(25) and in another one for panic disorder.(27) The identification of patients with anxiety disorders was conducted in two studies, (26, 27) with DSM III, DSM IV, and ICD-9 criteria,(31-33) another five studies used scales,(23-25, 28, 30) and diagnoses recorded in primary care notes were used in another study.(29) The follow up time ranged from ten to 22 years and the proportion of incidents strokes observed ranged from 0.2 to 12.6% with larger proportions of strokes observed in studies with longer follow up.(28, 30) Three studies excluded patients with past medical history of stroke,(25, 28, 29) two excluded patients with history of stroke in the year before study entry,(26, 27) and one excluded those with past medical history of cardiovascular disease.(24) The eight papers studied potential associations between anxiety and all types of strokes. One study observed only the association between anxiety and non-fatal strokes.(29) Another one reported the associations of anxiety with all types of strokes, and specifically with ischaemic strokes, which were not significant in either analyses.(30)

Three papers reported a significantly increased risk of stroke in patients with anxiety,(26-28) out of which one study reported also a dose–response relation, with a 17% increased risk of stroke for every standard deviation increase in anxiety.(28) A significantly increased pooled risk of stroke for patients with anxiety disorders was observed, with an overall hazard ratio (HR) estimated from the meta-analysis: 1.24 (95% CI: 1.09-1.41) p=0.001 (Figure two).

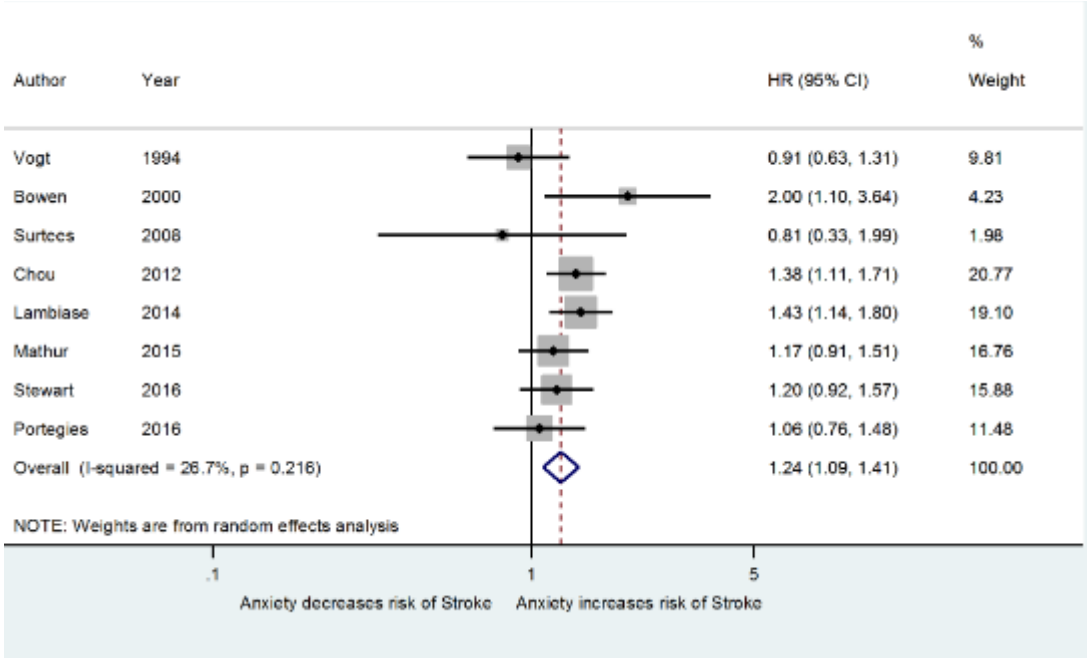

Figure 2: Pooled risk of stroke in patients with anxiety disorders

Heterogeneity between studies was low and not significant, I-squared index was 26.7% (p=0.216).(21) Sensitivity analysis excluding the studies by Vogt and colleagues,(23) Stewart and colleagues,(24) and both at the same time, only altered the magnitude of the pooled estimate by a negligible amount and the heterogeneity remained insignificant. The removal of the study by Surtees and colleagues(25) increased the heterogeneity to I-Squared 29.7%, but had negligible impact on the pooled estimate and its 95% confidence intervals. The funnel plot demonstrated a reasonable symmetry suggesting that publication bias, and other sources of biases due to methodology, quality, and small studies effect are unlikely (Figure three).

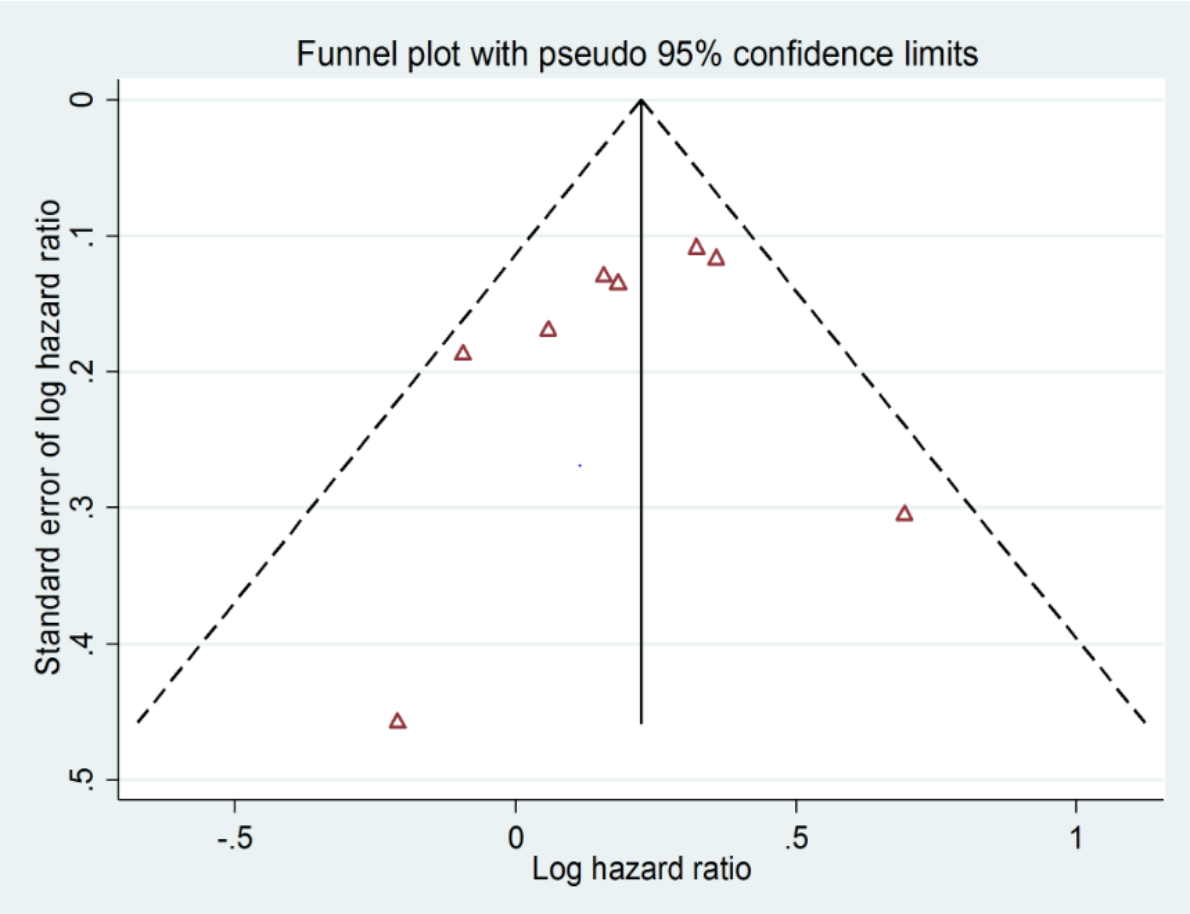

Figure 3. Funnel plot of studies included in this review

In two papers, after examination of the HRs for each year of follow up, the time between symptoms of anxiety and risk stroke was investigated. One of them reported an increased risk of stroke only within three years of the detection of anxiety, HR: 2.55 (1.45–4.46) but not in the longer term.(30) The other paper did not find an association between anxiety and stroke but reported an increased risk for cardiovascular disease (myocardial infarction or stroke) within three years of the detection of anxiety, but not in the longer term (24) They both suggest a possible short-term effect for anxiety symptoms on the risk of stroke.

Three papers explored the role of cardiovascular risk factors in the association between anxiety and stroke (28-30) Only one of them observed an association between anxiety and stroke, which became weaker but remained significant after adjusting for blood pressure,

cholesterol, diabetes mellitus, body mass index, alcohol use, physical activity, smoking, and antihypertensive medication, in a multivariable model.(28)

Three papers explored the role of depression in the association between anxiety and stroke. In all three the risk of stroke was not increased for patients with anxiety and this did not change when depression was included in the models.(24, 29, 30) None of the studies included in this review explored biological explanatory factors for the association between anxiety and stroke, such as inflammatory markers.

4. Discussion

The risk of stroke among patients with anxiety disorders has been investigated in a limited number of cohort studies, which were considered to be of good quality. The meta-analysis provides strong evidence for an association between anxiety and stroke, with a pooled risk of stroke increased by 24% among patients suffering anxiety disorders. There is limited evidence suggesting that the risk of stroke may be higher within three years of the diagnosis of anxiety, and that the risk of stroke may be further increased for patients with severe anxiety.

The evidence on the explanatory factors for the association between anxiety disorders and stroke is still limited. The increased prevalence of cardiovascular risk factors observed in patients with anxiety disorders may explain their higher risk of stroke (9, 34, 35) However, the only study that reported a significant association between anxiety and stroke, and adjusted at a later stage for cardiovascular risk factors, reported that the association became weaker but remained significant.(28) This suggests that cardiovascular risk factors do not fully explain the increased risk of stroke among patients with anxiety disorders. Therefore, a biological link between anxiety and stroke could also be considered. This would include the association of anxiety disorders with abnormal heart rhythm, raised inflammatory

markers, dysfunctions of the hypothalamic pituitary adrenal axis, and an increased risk of developing carotid plaques or arterial stiffness. Persistent estates of anxiety induce a hypothalamic-pituitary-adrenal hyperactivity with continuous sympathetic nervous system activation. The elevation of several neuropeptides results in a high blood pressure and arrhythmias, and the release of cytokines has pro-inflammatory and pro-coagulant effects on endothelium. The persistent high levels of cortisol may also lead to a downregulation of the hypothalamic pituitary adrenal axis and contribute to abnormal lipid profiles.(10, 36-39)

The lack of significant association between anxiety and stroke, observed in five papers, may be related to the long follow up of these studies. The association may be underestimated by the observation of patients long time after the diagnosis of anxiety, when the risk of stroke may not be increased.

The results of this review are consistent with a retrospective multicentre study which reported that psychosocial stress was associated with high risk of stroke.(40) This systematic review builds on a previous article (16) that using a different inclusion criteria, reported an association between anxiety and stroke across a number of papers, not including four recent studies which observed over half a million patients.(24, 28-30)

The different measures of anxiety used across the studies may have affected the final results. The DSM criteria, used in two studies, is considered the gold standard to diagnose anxiety.(41) The scales used in three studies (24, 25, 30) were all validated against the DSM criteria.(41, 42) The scales used in another two studies (23, 28) were also specifically developed to measure anxiety disorders.(28, 43) Finally, the study that used medical records to categorize participants as anxiety patients was based in the UK, where the national guidelines recommend the use of a scale that has also been validated against DSM criteria.(44, 45) Therefore, in all eight studies the diagnosis of anxiety was assisted with a diagnostic tool, which gives, according to a recent systematic review, a sensitivity 67% and

specificity of 88%.(46) The proportion of patients wrongly categorized may have resulted in an underestimation of the risk between anxiety and stroke, which could be stronger than the one observed.

This review has some limitations. The diversity of the methods across studies, including the different statistical management, may have an effect on the external validity of each individual one. Furthermore, only one person extracted most of the data (MPP). Even so, all data were checked for accuracy on multiple occasions. The availability of only eight studies represents another limitation of this review. This study has some strengths as well. The comprehensive search and critical assessment of studies conducted in this review allows estimation of the association between anxiety disorders and stroke obtained on a large number of patients. The use of a random effect model based on the assumption that studies were independently conducted and do not necessarily share a common effect size, allowing for more uncertainty of the final summary estimate was a conservative choice. The overall estimate remained significant despite the increased width of the confidence intervals, providing support to the significance of the findings. The reasonably symmetrical funnel plot supports the theory that there is no publication bias. While this is re-assuring, the plots may also be used to assess "small study effects", where smaller studies in a meta-analysis tends to show larger effects.(47) Although all the studies included were large, nonetheless they do vary in size. The funnel plot highlighted the random distribution of the estimates, indicating that large effects were not associated with smaller studies.

5. Conclusion

Clinicians should consider the relevance of anxiety disorders, which are not only a distressing problem on their own, but also predictors of coronary artery disease,(11) and stroke. Many patients have little understanding of the association between anxiety and

physical disease,(48) therefore clinicians may have to highlight this link to help patients understand the clinical relevance of anxiety disorders. Given the high prevalence of anxiety disorders,(1-3) the magnitude of their association with major cardiovascular events, and provided that they are a treatable conditions, interventions on anxiety disorders should have a positive impact on the incidence of both coronary artery disease and stroke.

Future studies on the risk of stroke in patients with anxiety disorders, and the explanatory factors for this association, are required in order to confirm, modify and/or expand these results. It is not possible to differentiate, with the available evidence, the risk of stroke associated with different anxiety disorders which may not be similar for panic disorders, agoraphobia, or other anxiety disorders. Therefore, the association between the different types of anxiety disorders, of different degrees of severity, and stroke, remains a matter for further research. Future studies may also address the impact of anxiety disorders, on specific types of stroke, which may vary for ischaemic and haemorrhagic ones. All these studies are needed to develop effective clinical and public health interventions for the treatment of anxiety disorders and the prevention of stroke. While a long follow up is normally considered a strength of observational research, future studies may look at stokes within three years of the diagnosis of anxiety, which seems to be the moment of highest risk.(24, 30)

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Appendix A: MOOSE Statement - Reporting Checklist for Authors of Meta-analyses of Observational Studies

Reporting Criteria	Reported	Reported on Page
Reporting of Background	Yes	5
Problem definition	Yes	5
Hypothesis statement	Yes	5
Description of Study Outcome(s)	Yes	5
Type of exposure or intervention used	Yes	5
Type of study design used	Yes	5
Study population	Yes	5
Reporting of Search Strategy	Yes	Supplement 2
Qualifications of searchers (eg, librarians and investigators)	Yes	6
Search strategy, including time period included in the synthesis and keywords	Yes	6 and Supplement 2
Effort to include all available studies, including contact with authors	Yes	6 and 7
Databases and registries searched	Yes	6
Search software used, name and version, including special features used (eg, explosion)	Not applicable	-
Use of hand searching (eg, reference lists of obtained articles)	Yes	6
List of citations located and those excluded	Yes	Table 1 and Figure 1
Method for addressing articles published in languages other than English	Not applicable	-
Method of handling unpublished studies	Not applicable	-
Description of any contact with authors	Yes	6
Reporting of Methods	Yes	6, 7 and 8
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	6 and 7
Rationale for the selection and coding of data	Yes	7
Documentation of how data were classified and coded	Yes	7
Assessment of confounding	Yes	Table 1
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	7. and Supplement 3
Assessment of heterogeneity	Yes	7
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	7
Provision of appropriate tables and graphics	Yes	Table 1. Figures 2 and 3

Reporting of Results	Yes	8,9,10 and 11
Table giving descriptive information for each study included	Yes	Table 1
Results of sensitivity testing	Yes	10
Indication of statistical uncertainty of findings	Yes	10
Reporting of Discussion	Yes	11, 12, 13 and 14
Quantitative assessment of bias (eg, publication bias)	Yes	10
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	6
Assessment of quality of included studies	Yes	Supplement 3
Reporting of Conclusions	Yes	12, 13 and 14
Consideration of alternative explanations for observed results	Yes	12
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	13
Guidelines for future research	Yes	14
Disclosure of funding source	Yes	14

Appendix B: Search Strategy

1- Anxiety
2- Anxiety disorder
3- Panic
4- Panic attacks
5- Agoraphobia
6- Phobic disorders
7- Phobic anxiety
8- Phobia
9 - Cerebrovascular disorders
10- Stroke
11- Cerebrovascular
12- Cerebral vascular
13- Cerebral
14- Cerebellar
15- Brain
16- Vertebrobasilar
17- Infarct*
18- Ischemi*
19- Ischaemi*
20- Thrombosis
21- Emboli*
22- Apoplexy
23- Intracerebral
24- Intracranial
25- Subarachnoid
26- Haemorrhage
27- Hemorrhage
28- Bleed*
29- 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
30- 9 OR 10 OR 11 OR 12
31- 13 OR 14 OR 15 OR 16
32- 17 OR 18 OR 19 OR 20 OR 21 OR 22
33- 31 AND 32
34- 13 OR 15 OR 23 OR 24 OR 25
35- 26 OR 27 OR 28
36- 34 AND 35
37- 30 OR 33 OR 36
38- 29 AND 37

Appendix C. Quality assessment of studies

	Scottish Intercollegiate Guidelines Network. Methodology Checklist 3: Cohort studies								
Guideline topic: Anxiety and risk of stroke		Reviewer:	María Pérez-Piñar						
Study identification (*Include author, title, year of publication, journal title, pages*)			Vogt 1994	Bowen 2000	Surtees 2008	Chou 2012	Lambiase 2014	Mathur 2015	Portegies 2016	Stewart 2016
Before completing this checklist, consider:			Y	Y	Y	Y	Y	Y	Y	Y
1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.										
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..			Y	Y	Y	Y	Y	Y	Y	Y
Reason for rejection: 1. Paper not relevant to key question □ 2. Other reason □ (please specify):			NA	NA	NA	NA	NA	NA	NA	NA
Section 1: Internal validity										
In a well conducted cohort study:		***Does this study do it?***								
1.1	The study addresses an appropriate and clearly focused question.[i]	Yes/No/Can't say	Y	Y	Y	Y	Y	Y	Y	Y
Selection of subjects										
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.[ii]	Yes/No/Can't say/Does not apply	Y	Y	Y	Y	Y	Y	Y	Y

1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.[iii]	Yes/No/Does not apply	Y	NA	N	NA	N	NA	Y	Y
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.[iv]	Yes/No/Does not apply	N	Y	N	N	Y	Y	N	Y
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.[v]		Y	N	N	N	Y	N	Y	Y
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.[vi]	Yes/No/Does not apply	N	NA	NA	NA	N	NA	N	N
ASSESSMENT										
1.7	The outcomes are clearly defined.[vii]	Yes/No/Does not apply	Y	Y	Y	Y	Y	Y	Y	Y
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.[viii]	Yes/No/Does not apply	N	N	N	N	N	N	N	N

1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.[ix]	Yes/No/Does not apply	N	N	N	N	N	N	N	N
1.1	The method of assessment of exposure is reliable.[x]	Yes/No/Does not apply	Y	Y	Y	Y	Y	Y	Y	Y
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.[xi]	Yes/No/Does not apply	Y	Y	Y	Y	Y	Y	Y	Y
1.12	Exposure level or prognostic factor is assessed more than once.[xii]	Yes/No/Does not apply	Y	Y	Y	Y	N	N	N	N
CONFOUNDING										
1.13	The main potential confounders are identified and taken into account in the design and analysis.[xiii]	Yes/No/Does not apply	Y	Y	Y	Y	Y	Y	Y	Y
STATISTICAL ANALYSIS										
1.14	Have confidence intervals been provided?[xiv]	Yes/No	Y	Y	Y	Y	Y	Y	Y	Y
2.1	How well was the study done to minimise the risk of bias or confounding?[xv]	High quality (++) Acceptable (+) Unacceptable –	++	++	++	++	++	++	++	++

2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes/No/Does not apply	Y	Y	Y	Y	Y	Y	Y	Y
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes/No	Y	Y	Y	Y	Y	Y	Y	Y
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.									

[1] Unless a clear and well defined question is specified in the report of the review, it will be difficult to assess how well it has met its objectives or how relevant it is to the question you are trying to answer on the basis of the conclusions.

[1] This relates to **selection bias**.* It is important that the two groups selected for comparison are as similar as possible in all characteristics except for their exposure status, or the presence of specific prognostic factors or prognostic markers relevant to the study in question.

[1] This relates to **selection bias**.* The participation rate is defined as the number of study participants divided by the number of eligible subjects, and should be calculated separately for each branch of the study. A large difference in participation rate between the two arms of the study indicates that a significant degree of **selection bias*** may be present, and the study results should be treated with considerable caution.

[1] If some of the eligible subjects, particularly those in the unexposed group, already have the outcome at the start of the trial the final result will be subject to **performance bias.*** A well conducted study will attempt to estimate the likelihood of this occurring, and take it into account in the analysis through the use of sensitivity studies or other methods.

[1] This question relates to the risk of **attrition bias**.*The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop out rate is regarded as acceptable, but in observational studies conducted over a lengthy period of time a higher drop out rate is to be expected. A decision on whether to downgrade or reject a study because of a high drop out rate is a matter of judgement based on the reasons why people dropped out, and whether drop out rates were comparable in the exposed and

unexposed groups. Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study.

[1] For valid study results, it is essential that the study participants are truly representative of the source population. It is always possible that participants who dropped out of the study will differ in some significant way from those who remained part of the study throughout. A well conducted study will attempt to identify any such differences between full and partial participants in both the exposed and unexposed groups. This relates to the risk of **attrition bias**.* Any unexplained differences should lead to the study results being treated with caution.

[1] This relates to the risk of **detection bias**.* Once enrolled in the study, participants should be followed until specified end points or outcomes are reached. In a study of the effect of exercise on the death rates from heart disease in middle aged men, for example, participants might be followed up until death, or until reaching a predefined age. **If outcomes and the criteria used for measuring them are not clearly defined, the study should be rejected.**

[1] This relates to the risk of **detection bias.*** If the assessor is blinded to which participants received the exposure, and which did not, the prospects of unbiased results are significantly increased. Studies in which this is done should be rated more highly than those where it is not done, or not done adequately.

[1] This relates to the risk of **detection bias.*** Blinding is not possible in many cohort studies. In order to assess the extent of any bias that may be present, it may be helpful to compare process measures used on the participant groups - e.g. frequency of observations, who carried out the observations, the degree of detail and completeness of observations. If these process measures are comparable between the groups, the results may be regarded with more confidence.

[1] This relates to the risk of **detection bias.*** A well conducted study should indicate how the degree of exposure or presence of prognostic factors or markers was assessed. Whatever measures are used must be sufficient to establish clearly that participants have or have not received the exposure under investigation and the extent of such exposure, or that they do or do not possess a particular prognostic marker or factor. Clearly described, reliable measures should increase the confidence in the quality of the study

[1] This relates to the risk of **detection bias.*** The primary outcome measures used should be clearly stated in the study. **If the outcome measures are not stated, or the study bases its main conclusions on secondary outcomes, the study should be rejected.** Where outcome measures require any degree of subjectivity, some evidence should be provided that the measures used are reliable and have been validated prior to their use in the study.

[1] This relates to the risk of **detection bias.*** Confidence in data quality should be increased if exposure level is measured more than once in the course of the study. Independent assessment by more than one investigator is preferable.

[1] Confounding is the distortion of a link between exposure and outcome by another factor that is associated with both exposure and outcome. The possible presence of confounding factors is one of the principal reasons why observational studies are not more highly rated as a source of evidence. The report of the study should indicate which potential confounders have been considered, and how they have been assessed or allowed for in the analysis. Clinical judgement should be applied to consider whether all likely confounders have been considered. If the measures used to address confounding are considered inadequate, the study should be downgraded or rejected, depending on how serious the risk of confounding is considered to be. **A study that does not address the possibility of confounding should be rejected.**

[1] Confidence limits are the preferred method for indicating the precision of statistical results, and can be used to differentiate between an inconclusive study and a study that shows no effect. Studies that report a single value with no assessment of precision should be treated with extreme caution.

[1] Rate the overall methodological quality of the study, using the following as a guide: **High quality** (++): Majority of criteria met. Little or no risk of bias. Results unlikely to be changed by further research. **Acceptable** (+): Most criteria met. Some flaws in the study with an associated risk of bias, Conclusions may change in the light of further studies. **Low quality** (0): Either most criteria not met, or significant flaws relating to key aspects of study design. Conclusions likely to change in the light of further studies.

3.2 Factores de Riesgo Cardiovascular en pacientes con patología psiquiátrica

Los artículos y las revisiones sistemáticas contenidas en la sección anterior mencionan casi de modo unánime la escasa evidencia que existe acerca de los mecanismos de asociación entre la patología psiquiátrica y cardiovascular. Una de las hipótesis más consistentes es que los pacientes con problemas de salud mental tienen un mayor riesgo de desarrollar factores de riesgo cardiovascular, lo que llevaría finalmente a presentar patologías como el ictus o la cardiopatía isquémica. En esta sección se revisa la literatura existente sobre la prevalencia de factores de riesgo cardiovascular en pacientes con patología psiquiátrica.

Una revisión sistemática publicada en 2012 observó un riesgo aumentado de desarrollar hipertensión arterial en pacientes con diagnóstico previo de depresión.[43] Otras dos revisiones de 2014 y 2015 encontraron un riesgo aumentado en estos pacientes de padecer diabetes[44, 45] aunque sólo una de ellas revisó estudios prospectivos,[44] mientras que en la otra se incluyeron estudios transversales.[45] También se ha observado en estudios prospectivos un incremento en el riesgo de obesidad.[46] Finalmente se identificó una revisión de 2009 en que se observó un aumento del tabaquismo en adolescentes con diagnóstico previo de depresión.[47]

En 2014 se publicó otra revisión sistemática de estudios prospectivos que encontró una relación entre los trastornos de ansiedad y el tabaquismo.[48] De acuerdo a otra revisión, también de estudios prospectivos, de 2015 existiría también un riesgo aumentado de hipertensión en estos pacientes.[49]

Una revisión sistemática de estudios transversales del 2005 encontró un riesgo aumentado de tabaquismo en pacientes con esquizofrenia.[50] Dichos pacientes, según otra revisión de estudios transversales del 2008, también parecen tener un riesgo aumentado de diabetes.[14] En este mismo trabajo se observó un riesgo aumentado de diabetes, aunque no de hipertensión ni valores más altos de colesterol, entre pacientes con enfermedad mental

severa (esquizofrenia o enfermedad bipolar). La prevalencia aumentada de diabetes en esquizofrénicos ha sido confirmado en 2015 en otra revisión sistemática de estudios tansversales.[51] Otra revisión, que incluye estudios transversales de personas con psicosis, observó un incremento de comportamientos sedentarios entre estos pacientes.[52] También se ha observado en una revisión sistemática de estudios transversales publicada en 2015 que los pacientes con enfermedad mental severa tienen una mayor prevalencia de síndrome metabolico.[53] Los pacientes con enfermedad bipolar fueron estudiados específicamente en una revisión del mismo autor, también de estudios transversales, publicada en 2015, y se observó su riesgo significativamente aumentado de padecer diabetes.[54] Diversos estudios originales han observado el mayor riesgo de hipertensión, hiperlipidemia, o síndrome metabólico en estos pacientes.[55-57]

La tablas 3.2.1, 3.2.2, 3.2.3 y 3.2.4 presentan las características de las revisiones que han estudiado factores de riesgo cardiovascular entre pacientes con patología psiquiátrica.

	Resulted (N studios)	**Riesgo. Promedio ponderado**	**Países**	**N**	**Seguimiento (años)**	**Sugerencias para investigación futura**
Chaiton 2009	Tabaquismo (12)	1.41 (1.21-1.63)	EEUU Australia N-Zelanda China	522-8704	1-21	Mecanismos de la asociación entre la depresión y el tabaquismo
Luppino 2010	Obesidad (9)	1.58 (1.33-1.87)	--	447-44396	5-22	Nuevos estudios prospectivos que investiguen mecanismos de asociación entre distintos tipos de depresión y obesidad
Meng 2012	HTA (9)	1.42 (1.09-1.86)	Canada EEUU Finlandia Rusia	230-7643	1.6-15	Nuevos estudios ajustados para factores de riesgo que observen el riesgo de HTA en pacientes con depresión
Hasan 2014	DM (16)	1.45 (1.12-1.87)	EEUU España Holanda Noruega Suecia Japón Taiwán	--	3-15.6	Estudios prospectivos con ajuste para factores de confusión. Estudios en países de ingreso bajo
Vancampfort 2014	DM (18)	1.33(1.03-1.73)	--	5531 (entre todos los estudios)	--	Riego de DM en distintos tipos de depresión. Riesgo de DM según régimen de tratamiento para la depresión Estudio de desigualdades en el tratamiento de la DM en estos pacientes Estudios con seguimiento largo

Tabla 3.2.1 Revisiones sistemáticas sobre factores de riesgo cardiovascular en pacientes con depresión HTA: Hipertensión arterial. DM: Diabetes Mellitus

	Resulted (N studios)	**Riesgo. Promedio ponderado**	**Países**	**N**	**Seguimiento (años)**	**Sugerencias para investigación futura**
Jiang 2014	Tabaquismo (15)	1.58(1.45-1.73)	America Europa Oceania	814-2129	20-21	Nuevos estudios prospectivos. Mecanismos de asociación entre ansiedad y tabaquismo
Pan 2015	HTA (8)	1.55 (1.24-1.94)	Canada EEUU Dinamarca Holanda	330-75268	1-20	La asociación a corto y largo plazo entre la ansiedad y la HTA. La asociación bidireccional. Los mecanismos de asociación

Tabla 3.2.2 Revisiones sistemáticas sobre factores de riesgo cardiovascular en pacientes con ansiedad. HTA: Hipertensión arterial.

	Resultados (N studios)	**Riesgo. Promedio ponderado**	**Países**	**N**	**Seguimiento (años)**	**Sugerencias para investigación futura**
De Leon 2005	Tabaquismo (42)	5.9 (4.9-5.7)	Canadá Chile Colombia EEUU Alemania España Finlandia Francia Gracia Irlanda Israel RUnido Suecia Suiza Turquía Japón Singapur Taiwán Australia	--	--	Estudios que comparen tasa de abandono de tabaquismo en mujeres con y sin esquizofrenia
Osborn 2008	DM (8)	1.87 (1.68-2.09)	--	--	--	Estudios prospectivos con muestras grandes
Stubbs 2015	DM (25)	1.82 (1.56-2.13)	Canadá EEUU España Finlandia R Unido China India Japón Singapur Taiwán Australia	--	--	Mecanismos de la asociación entre la esquizofrenia y la diabetes en especial la relevancia de los antipsicóticos
Vancampfort 2015	Síndrome metabólico (93)	33.4 (30.8-36.0)	Brasil Canadá EEUU Alemania España Croacia Holanda Corea del sur India Australia	29596 (entre todos los estudios)	--	--
Stubbs 2016	Sedentarismo (13)	2.80 (1.47-4.1)	Canadá EEUU Bélgica Holanda Portugal RUnido Australia	8-1277	--	Estudios prospectivos con muestras grandes de pacientes de la población en vez de seleccionados para el estudio

Tabla 3.2.3 Características de las revisiones de estudios sobre factores de riesgo cardiovascular en pacientes con esquizofrenia. DM: Diabetes Mellitus

	Resultados (N studios)	Riesgo. Promedio ponderado	Países	N	Seguimiento (años)	Sugerencias para investigación futura
Van camp fort 2015	Síndrome metabólico (33)	31.7(27.3-36.3)	Brasil Canadá EEUU Alemania España Croacia Holanda Corea del sur India Australia	5827 (entre todos los estudios)	--	Estudios prospectivos con seguimiento largo. Mecanismo de asociación
Van camp fort 2015	DM(19)	1.98(1.6-2.4)	--	18060 (entre todos los estudios)	--	Mecanismos de asociación

Tabla 3.2.4 Características de las revisiones de estudios sobre factores de riesgo cardiovascular en pacientes con enfermedad bipolar.

DM: Diabetes Mellitus

Los trastornos de personalidad han recibido menor atención por parte de los investigadores que otras patologías psiquiátricas y no se encontraron revisiones sistemáticas sobre factores de riesgo cardiovascular en estos pacientes. Un estudio reciente observo un aumento del riesgo de obesidad en adultos que habían sido diagnosticados de trastorno de personalidad en la adolescencia.[58] Otros estudios han observado un riesgo incrementado de diabetes y tabaquismo.[59, 60]

En resumen, existe un cierto número de revisiones sistemáticas, que reflejan una mayor incidencia o prevalencia de factores de riesgo cardiovascular en pacientes con algunos problemas psiquiátricos. La patología mental más estudiada es la depresión, seguida de la esquizofrenia. La evidencia es más escasa para los trastornos de ansiedad y la enfermedad bipolar y llamativamente pobre para pacientes con trastornos de personalidad. El factor de riesgo cardiovascular que ha recibido más atención por parte de investigadores, en el

contexto de la patología psiquiátrica es la diabetes, seguida del tabaquismo. El número de estudios que abordan la hipertensión, la obesidad, el síndrome metabólico y el sedentarismo es menor.

En medicina de familia en muchas ocasiones se toman decisiones clínicas que no dependen de factores de riesgo individuales. Muchas pautas de manejo, incluida la prescripción de estatinas,[61] están basadas en la estimación del riesgo que un paciente tenga de sufrir un evento cardiovascular en los años siguientes, y dichas estimaciones están calculadas sobre un conjunto de factores de riesgo.[62] No se encontraron revisiones sistemáticas sobre estimaciones de riesgo cardiovascular en pacientes con problemas psiquiátricos. Para cubrir esta área de evidencia pobre se decidió llevar a cabo una revisión de estudios que observaran diferencias en el riesgo cardiovascular entre personas con y sin patología psiquiátrica. Sin embargo, antes de empezar a revisar la literatura se observó en el *International Prospective Register of Systmeatic Reviews*[63] que un equipo del Institut Universitari d'Investigació en Atenció Primària Jordi Gol de Barcelona estaba llevando a cabo la revisión que yo había pensado realizar. Contactamos con el autor de correspondencia de dicho proyecto. La revisión sistemática estaba aún en sus fases iniciales. Se planteó entonces la posibilidad de colaborar con ellos, a lo cual respondieron positivamente. La colaboración con el Institut Universitari d'Investigació en Atenció Primària Jordi Gol de Barcelona se mantuvo tras terminarse esta revisión y uno de sus investigadores colaboró en los demás trabajos que presento en esta tesis.

La revisión sistemática que presento en esta sección, dirigida por los investigadores del Institut Universitari d'Investigació en Atenció Primària Jordi Gol de Barcelona, y en la que yo he participado, ha sido publicada en *BMC Psychiatry*. Un póster basado en esta revisión se presentó en el XXV congreso de Atención Primaria de la Sociedad Catalana de Medicina

Familiar y Comunitaria celebrado en Tarragona el 5 de noviembre de 2015. Dicho póster está presentado a continuación del artículo (figura 3.3.1).

Cardiovascular risk assessment in patients with a severe mental illness: a systematic review and meta-analysis

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5- The Westborough Road Health Centre. Westcliff-on-Sea. United Kingdom

6- Centre of Primary Care and Public Health. Queen Mary University of London. United Kingdom

7- Instituto de Neuropsiquiatría y Adicciones (INAD), Hospital del Mar Parc de Salut Mar. Departamento de Psiquiatría y Medicina Legal, Universitat Autònoma de Barcelona. Spain

8. Gimbernat School of Nursing. Universitat Autònoma de Barcelona. Spain

Abstract

Background Cardiovascular risk (CVR) has been observed to be higher in patients with severe mental illness (SMI) than in the general population. However, some studies suggest that CVR is not equally increased in different subgroups of SMI. The purposes of this review are to summarise CVR scores of SMI patients and to determine the differences in CVR between patients with different SMIs and between SMI patients and the control-population.

Methods MEDLINE (via PubMed) was searched for literature published through August 28, 2014, followed by a snowball search in the Web of Science. Observational and experimental studies that reported CVR assessments in SMI patients using validated tools were included. The risk of bias was reported using STROBE and CONSORT criteria. Pooled continuous data were expressed as standardized mean differences (SMD) with 95% confidence intervals (CI). Two reviewers independently selected studies, extracted data and assessed methodological quality.

Results A total of 3,608 articles were identified, of which 67 full text papers were assessed for eligibility and 35 were finally included in our review, in which 12,179 psychiatric patients and 225,951 comparative patients had been assessed. The most frequent diagnoses were schizophrenia and related diagnoses (45.7%), depressive disorders (14.7%), SMI (11.4%) and bipolar disorders (8.6%). The most frequent CVR assessment tool used was the Framingham risk score. Subgroups analysis showed a higher CVR in schizophrenia than in depressive disorder or in studies that included patients with multiple psychiatric diagnoses (SMD: 0.63, 0.03, and 0.02, respectively)

Six studies were included in the meta-analysis. Total overall CVR did not differ between SMI patients and controls (SMD: 0.35 [95% CI: -0.02 to 0.71], p=0.06); high heterogeneity was observed (I^2=93%; p<0.001).

Conclusions The summary of results from studies that assessed CVR using validated tools in SMI patients did not find sufficient data (except for limited evidence associated with schizophrenia) to permit any clear conclusions about increased CVR in this group of patients compared to the general population.

The systematic review is registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/): CRD42013003898.

Keywords Cardiovascular risk; severe mental illness; depressive disorder; bipolar disorder; schizophrenia; systematic review

Background

Cardiovascular disease is the leading cause of overall mortality, accounting for 24% of deaths worldwide, while psychiatric diseases, led by major depressive disorder, are considered the eleventh most burdensome disease globally, with an increasing effect on overall mortality [1,2].

Criteria for the definition of severe mental illness (SMI) differ, with some authors applying a narrow definition based on psychosis [3] and others also including a set of nosological entities of different types and clinical symptoms but with several common diagnostic criteria: severity, persistence over time (two years or more), and a tendency toward clinical deterioration and difficulties in social and occupational function [4,5].

It has been reported that cardiovascular risk (CVR) is higher in patients with SMI [6]. Studies in patients with bipolar disorder and schizophrenia indicate that they have a higher CVR than in the general population [7]. In patients with schizophrenia, the most prevalent CVR factors are smoking (71%), hypercholesterolemia (66%), hypertriglyceridemia (26%), hypertension (18%) and diabetes (5%) [8]. Risk of metabolic syndrome is also higher among patients with schizophrenia and bipolar disorder [9]. Moreover, patients with anxiety and major depression have higher prevalence of hypertension compared to groups of similar age from the general population [10,11].

Several factors may contribute to this raised CVR among patients with SMI, including unhealthy behaviours, difficulties in communication, barriers to medical care, poor treatment adherence and social deprivation [12]. Patients with SMI often receive fragmented medical care and fewer preventive measures, which leads to higher levels of underdiagnosis and lower rates of disease control [13]. Furthermore, antipsychotic drugs, antidepressants, and mood-stabilizing drugs have deleterious side effects, including important cardiometabolic consequences [14-16].

However, to date no systematic analysis has investigated whether CVR is increased equally in all patients with SMI, making it difficult to design and implement effective, feasible, evidence-based interventions for CVR management in these patients. A summary of the observations about CVR in the different subgroups of patients with SMI would provide a better epidemiological description of the problem, inform more effective clinical and preventive strategies, and help in the design of further studies.

The major aim of this review was to summarize the available evidence of CVR scores in patients with SMI. Furthermore, this review attempted to determine whether CVR differs between subgroups of SMI patients and compare the CVR between patients with SMI and the general or non-psychiatric population.

Methods

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria were used to undertake this review and meta-analysis [17], together with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. We conducted a systematic review of studies that reported CVR in patients with SMI.

Eligibility criteria

We included studies that reported CVR scores in patients with SMI. The following 10 diagnoses were included in the search strategy: schizophrenic disorders, schizotypal disorders, persistent delirious disorders, induced delirious disorders, schizoaffective disorders, other non-organic psychotic disorders, bipolar disorder, serious depressive episode with psychotic symptoms, recurrent serious depressive disorders, and compulsive obsessive disorder [5].

We included observational and experimental studies that applied validated CVR tools, including Framingham risk score (FRS) with its subtypes of scores (cardiovascular disease (CVD), cardiovascular heart disease (CHD), Myocardial infarction (MI) and the Systematic Coronary Risk Evaluation (SCORE). If the studies reported data on other CVR scores not described above, these were also included.

We excluded articles that were based on first episodes of SMI, different reports from the same population (selecting the study with the most recent publication date or the largest sample size), papers reporting diagnoses based on symptoms, and studies referring to one or two psychotropic drugs.

Search strategy

We conducted a systematic search in PubMed using a combination of MESH and free text terms (Table 1). We searched from inception to the August 28, 2014. Based on the articles selected, we performed a snowball search in the Web of Science. We reviewed all the references (backward search) and the articles that cited the included papers (forward search). In addition, we added articles that were identified during the implementation of the review (hand searching). There were no language restrictions.

Database	Search Strategy	References
PubMed	("Psychotic Disorders"[Mesh] OR "Bipolar Disorder"[Mesh] OR "Schizophrenia"[Mesh] OR psychotic OR psychosis OR psychoses OR schizo* OR bipolar OR manic OR mania OR delirious OR depress* OR obsessive-compulsive OR "obsessive compulsive" OR "compulsive obsessive" OR OCD OR agoraphob* OR panic OR phobia OR phobic OR melanchol* OR neurosis OR neurotic OR neuroses OR conversion disorder* OR "Mental Disorders" OR "severe mental") AND (cardiovascular OR "Cardiovascular diseases" OR CVD) AND (risk score* OR risk chart* OR "risk prediction" OR risk check* OR "risk assessment" OR "risk evaluation" OR "risk calculator" OR risk-estimation OR "risk estimation" OR "year risk" OR "year CVD risk" OR Framingham OR "SCORE risk" OR SCORE chart* OR SCORE table* OR "Systematic Coronary Risk Evaluation" OR "REGICOR" OR "REGICOR table"* OR ASSIGN OR QRISK OR PROCAM OR WHO/ISH)	653
Web of Science	Snowballing: references cited in the eligible papers (forward), and references citing the eligible papers (backward)	2,955

Table 1. Search Strategies for the Electronic Databases (data retrieved August 28, 2014)

Study selection

Two researchers (CVF and QFB) reviewed the titles and abstracts of all studies identified in the initial search and defined a list of full text articles to be assessed. Cases of discordance were resolved by consensus; when necessary, the full-text article was reviewed. We conducted a pilot test of the eligibility criteria on a sample of 15 articles. We used this test to clarify these criteria and ensure that they were applied consistently by all reviewers. Primary outcome was the CVR assessed with any validated CVR tool.

Data collection

We used a standardized data-collection form to record author and publication year, study design, country, setting, diagnosis, diagnostic criteria, number of participants and age in the psychiatric group and the comparative group (if applicable) and the objective of the study. To assess the methodological quality of the studies, we used the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) checklist for observational studies, with a maximum possible score of 24 [19], and the Consolidated Standards of Reporting Trials (CONSORT) for randomized trials, with a maximum possible score of 37 [20], giving one point for each item the article addressed.

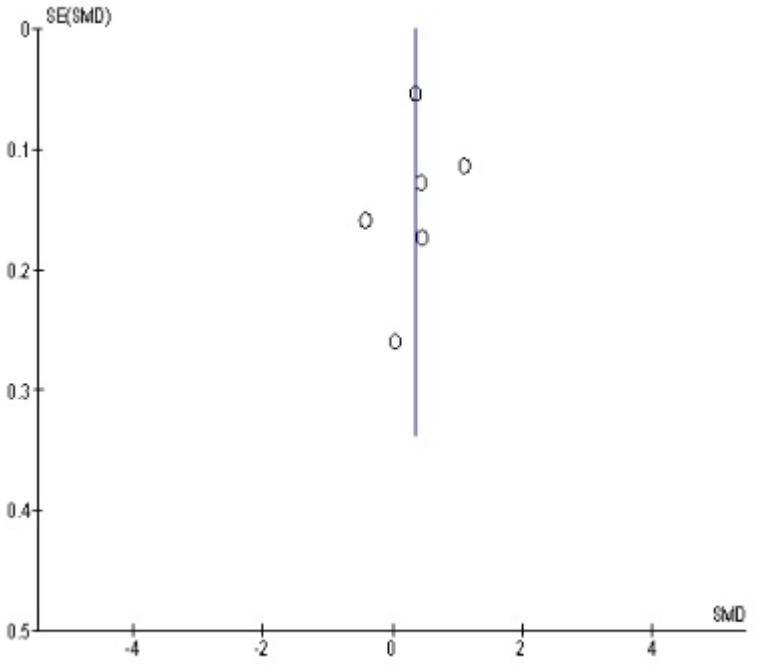
Two reviewers assessed methodological quality and extracted the data independently. Discrepancies were resolved by consensus between the two reviewers (CVV and QFB) and by discussion with a third reviewer (MFS) as needed. Inter-rater agreement was 96%.

Statistical analysis

We analysed outcomes using Review Manager (RevMan, version 5.3). Pooled continuous data were expressed as standardized mean differences (SMD) with 95% confidence

intervals (CI). The effect size (ES) was categorized as small (< 0.2), small to moderate (0.2-0.5), moderate to large (0.51-0.79), large (> 0.79). Pooled SMD were estimated by using an inverse-variance-weighted random-effects model. Heterogeneity was quantified with the I^2 statistic, which describes the proportion of the total between-study variability due to heterogeneity [21]. We used subgroup analysis to evaluate whether results differed according to the diagnosis (depressive disorder, schizophrenia vs psychiatric diagnoses), diagnosis criteria (non-specific (NE) vs DSM IV), study design (observational vs randomized control trial); and outcome (cardiovascular disease, coronary heart disease, stroke)

We assessed publication bias by using funnel plots. In sensitivity analysis, we assessed the relative influence of each study on the pooled estimate by omitting one study at time. (Figure 2)



Abbreviations: SMD: Standardized mean difference, SE: Standard error.

Figure 2. Funnel plot

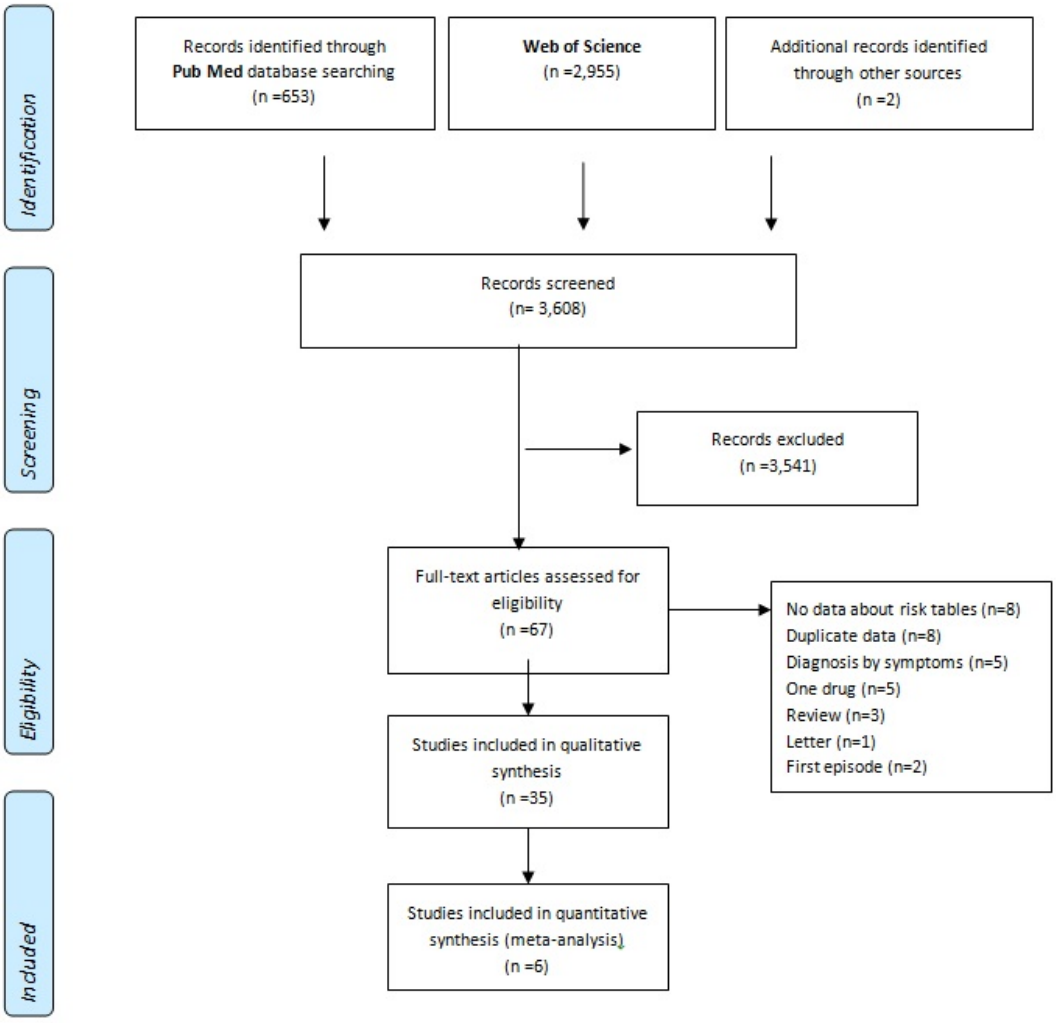
Protocol and registration

The initial protocol of the review was submitted to the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/PROSPERO/). The definitive protocol included the modifications suggested by the PROSPERO reviewers. The registration number of systematic review is: CRD42013003898.

Results

The electronic and manual searches retrieved 3,608 articles, of which 67 full-text papers were assessed for eligibility and 35 studies were finally included in our review (Figure 1), representing a total of 12,179 psychiatric patients and 225,951 controls.

Figure 1. Flow diagram of article review process



Sample size of psychiatric study groups ranged from 36 [23] to 1,942 [43] participants. Of the 35 studies, 19 studies in Eurasia (16 in Europe) and 16 studies were conducted in the Americas. The most common design was cross-sectional (22 studies); 8 studies were randomized controlled trials (RCT) and only 5 were case-control studies (Table 2). A 45.7% of the studies were performed in secondary services exclusively and 31.4% in the hospital setting. The most frequent diagnoses were schizophrenia and related diagnoses (45.7%), depressive disorders (14.3%), and bipolar disorders (8.6%). Seven studies

(20.0%) included different psychiatric diagnoses and only 4 (11.4%) showed data on SMI as a whole. In 30 studies, methodological quality was evaluated with STROBE and most showed a high quality score (median 21.00, SD: 6.40). Five were evaluated with CONSORT and most had a low quality score (median 18.57, SD: 2.72). The STROBE evaluation revealed two main weaknesses: insufficient efforts to address potential sources of bias and sparse information for each variable of interest on the number of participants with missing data. The CONSORT weaknesses were the method used to generate the random allocation sequence and type of randomisation; details of any restriction (such as blocking and block size); and information about where the full trial protocol can be accessed, if available.

Author, year	Study design	Country	Setting	Diagnosis	Diagnostic criteria
Acharya T, 2013 [22]	Retrospective cross-sectional	USA	Hospital	Depressive disorder	Not reported
Allan CL, 2011 [23]	Cross-sectional	UK	Primary & secondary care services	Depressive disorder	DSM IV
Arango C, 2008 [24]	Cross-sectional	Spain	Secondary services	Schizophrenia & related disorders	DSM IV
Bernardo M, 2009 [25]	Cross-sectional	Spain	Psychiatric hospital	Schizophrenia	DSM IV
Cohn T, 2004 [26]	Cross-sectional	Canada	Psychiatric hospital & secondary services	Schizophrenia & related disorders	DSM IV
Correll CU, 2006 [27]	Cross-sectional	USA	Psychiatric hospital	Psychiatric diagnosis	Not reported
Correll CU, 2011 [28]	Cross-sectional	USA	Psychiatric hospital	Psychiatric diagnosis	Not reported
Daumit GL, 2008 [29]	RCT	USA	Secondary services	Schizophrenia	DSM IV
Dickerson FB, 2013 [30]	RCT	USA	Secondary services	SMI	DSM IV
Druss BG, 2010 [31]	RCT	USA	Secondary services	SMI	Not reported
Ferreira L, 2010 [32]	Case-control	Portugal	Secondary services	Schizophrenia	DSM IV
Foguet-Boreu Q, 2013 [33]	Cross-sectional	Spain	Secondary services	SMI	Not reported
Garcia-Portilla MP, 2009 [34]	Cross-sectional	Spain	Secondary services	Bipolar disorders	ICD10
Goodrich DE, 2012 [35]	RCT	USA	Secondary services	Schizophrenia	Not reported
Goff DC, 2005 [36]	Case-control	USA	Secondary services	Schizophrenia	DSM IV
Grover S, 2014 [37]	Cross-sectional	India	Hospital	Bipolar disorder	ICD10
Hoffman BM, 2010 [38]	RCT	USA	Hospital	Depressive disorder	DSM IV
Jin H, 2011 [39]	Cross-sectional	USA	Secondary services	With psychotic symptoms	DSM IV
Mackin P, 2007 [40]	Case-control	UK	Secondary services	Psychiatric diagnosis	Not reported
Margari F, 2013 [41]	Cross-sectional	Italy	Psychiatric hospital	Psychiatric diagnosis	DSM IV
McCreadie RG, 2003 [42]	Cross-sectional	UK	Secondary services	Schizophrenia	DSM IV
McLean G, 2014 [43]	Cross-sectional	UK	Primary care	Schizophrenia & related disorders	Read code
Nurjono M, 2014 [44]	Cross-sectional	Singapore	Psychiatric hospital	Schizophrenia	DSM IV
Osborn DP, 2006 [45]	Cross-sectional	UK	Primary care	SMI	Not reported
Protopopova D, 2012 [46]	Cross-sectional	Czech Republic	Psychiatric hospital	Schizophrenia & pychoses	ICD10
Ratliff JC, 2013 [47]	Case-control	USA	Secondary services	Schizophrenia & related disorders	DSM IV
Said MA, 2012 [48]	Cross-sectional	Malaysia	Hospital	Schizophrenia	DSM IV
Stroup TS, 2013 [49]	RCT	USA	Secondary services	Schizophrenia & related disorders.	Not reported
Sicras-Mainar A, 2013 [50]	Cross-sectional	Spain	Primary, secondary & hospital care services	Schizophrenia & related disorders	DSM IV
Slomka JM, 2012 [51]	RCT	USA	Secondary services	Bipolar disorder	Not reported
Smith PJ, 2007 [52]	RCT	USA	Not reported	Depressive disorder	DSM IV
Tay YH, 2013 [53]	Cross-sectional	China	Secondary services	Schizophrenia	DSM IV
Taylor V, 2010 [54]	Case-control	Canada	Secondary services	Bipolar disorder & major depressive disorder	DSM IV
Wysokiński A, 2012 [55]	Retrospective review	Poland	Psychiatric hospital	Psychotic disorder	ICD10
Zuidersma M, 2015 [56]	Cross-sectional	Netherlands	Primary & secondary care services	Depressive disorder	DSM IV

Table 2. Characteristics of the studies included in the review (FRS: Framingham risk score, CVD: cardiovascular disease, CHD: cardiovascular heart disease, MI: myocardial infarction, SCORE: Systematic Coronary Risk Evaluation, NE: SMI: severe mental illness, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, ICD-10: International Classification of Diseases, 10th revision, RCT: randomized controlled trial.)

Of the 35 studies included, only 7 studies had control groups [23,36,40-42,47,53]. These studies used different scores to evaluate CVR (Table 3). Three studies included only patients with schizophrenia and controls: two studies were based on FRS (CVD) scores: 10.7 vs. 8.5 $p \leq 0.01$ [47] and 4.7 (4.7) vs. 3.1 (3.2), $p=0.002$ [53] and one was based on FRS (CHD) scores: 8.6 (7.3) vs. 6.3 (6.0), $p<0.001$ [36]. Two studies included psychiatric diagnoses and were based on FRS (CVD) scores: 11.3 (12.3) vs. 6.8 (6.4), $p<0.01$ [40] and 8.3 (5.8) vs. 10.7 (5.9), $p=0.05$ [41]. One study included depressive disorders: 10.3 (7.6) vs. 10.1 (7.7), $p=0.97$ [23]. One study had insufficient data and was not included in the meta-analysis.

Author, year	Psychiatric Group						Comparative Group				
	N	Age mean SD	FRS mean SD			Score mean SD	N	Age mean SD	FRS mean SD		
			CVD	Stroke	CHD				CVD	Stroke	CHD
Acharya T, 2013 [22]	1.136	60.1 (3.0)			By drug		472	61,4 (11.9)			17.1 (5.7)
Allan CL, 2011 [23]	36	71.8 (7.7)		10.3 (7.6)			25	71.8 (7.3)		10.1 (7.7)	
Arango C, 2008 [24]	1.452	40.7 (12.2)			6.8 (6.9)	0.9 (1.9)					
Bernardo M, 2009 [25]	733	37.8 (11.3)									
Cohn T, 2004 [26]	240	43.6 (1.3)					7,020	43.6 (1.3)			
Correll CU, 2006 [27]	367	42.9 (15.3)									
Correll CU, 2011 [28]	127	39.3 (14.9)			2.5 (4.2)						
Daumit GL, 2008 [29]	1.125	40.7 (11.1)			8.5 (7.4)						
Dickerson FB, 2013 [30]	291										
Druss BG, 2010 [31]	407										
Ferreira L, 2010 [32]	125	41.0 (11.0)					1,721	41.0 (12.0)			
Foguet-Boreu Q, 2013 [33]	137	51.1 (12.9)									
Garcia-Portilla MP, 2009 [34]	194	46.6			7.6 (7.4)	1.8 (4.4)					
Goodrich DE, 2012 [35]	134	52.8 (9.9)									
Goff DC, 2005 [36]	689	40.4 (11.2)					687	40.4 (11.2)			6.5
Grover S, 2014 [37]	105	39.6 (13.1)			3.4 (5.0)	1.7 (1.8)					
Hoffman BM, 2010 [38]	46	53.4 (7.0)	14.0 (9.0)								
Jin H, 2011 [39]	179	63.1									
Mackin P, 2007 [40]	90	45.7 (11.8)	11.3 (12.3)	1.7 (3.2)	9.3 (10.5)		92	43.5 (13.6)	6.8 (6.4)	1.0 (1.1)	4.7 (4.3)
Margari F, 2013 [41]	83	47.0 (9.0)	8.3 (5.8)				77	52.0 (8.6)	10.7 (5.9)		
McCreadie RG, 2003 [42]	102	45.0 (13.0)			9.5 (7.6)						4.1 (4.0)
McLean G, 2014 [43]	1.942						215,165				
Nurjono M, 2014 [44]	64										
Osborn DP, 2006 [45]	74						148				
Protopopova D, 2012 [46]	129	36.0 (11.9)									
Ratliff JC, 2013 [47]	115	47.5 (8.3)	10.7				197	47.7 (8.5)	8.5		
Said MA, 2012 [48]	270				6.3 (5.6)						
Stroup TS, 2013 [49]	215	41.1 (11.1)			7.3 (5.7)						
Sicras-Mainar A, 2013 [50]	705	48.2 (15.8)	11.9 (5.7)								
Slomka JM, 2012 [51]	118	53.0 (9.9)	13.7 (10.0)								
Smith PJ, 2007 [52]	198	51.6 (7.5)			5.4 (3.2)						
Tay YH, 2013 [53]	83	36.2 (7.7)	4.7 (4.7)				243	34.6 (8.2)	3.1 (3.2)		
Taylor V, 2010 [54]	54	25.9 (7.0)					104				
Wysokiński A, 2012 [55]	62	38.0 (12.4)	6.4 (7.2)	3.7 (2.8)	5.8 (6.1)						
Zuidersma M, 2015 [56]	352	70.7 (7.4)	5.8 (3.8)								

Table 3. Characteristics of the studies included in the review

Table 4 synthesized the data about CVR scores found in studies by diagnosis groups of diseases. The CVR mean score assessed with FRS (CVD) in patients with depression ranged from 5.8 to 14.0, in patients with schizophrenia from 4.7 to 11.9, and was 13.7 in the only study of patients with bipolar disorder. Studies that addressed patients with SMI reported that CVR had been expressed in different forms.

Diagnosis Groups	Author, year	Psychiatric Group				Notes
		FRS [mean (SD)]			Score	
		CVD	Stroke	CHD	mean SD	
Bipolar disorder	Grover S, 2014			3.4 (5.0)	1.7 (1.8)	
	Slomka JM, 2012	13.7 (10.0)				
	Garcia-Portilla MP, 2009			7.6 (7.4)	1.8 (4.4)	
Depressive disorder	Acharya T, 2013					FRS (CHD) expressed by types of antidepressive medication groups.
	Allan CL, 2011		10.3 (7.6)			
	Hoffman BM, 2010	14.0(9.0				
	Smith PJ, 2007			3.2		
	Zuidersma M, 2015	5.8 (3.8)				
Schizophrenia	Bernardo M, 2009					SCORE: <1%: 15.1%; 1-4%:68.8%; 5-10%: 6.1%; 11-15%:0.3% and ≥15%;0.1%
	Daumit GL, 2008			8.5 (7.4)		
	Ferreira L, 2010					SCORE: no significant difference observed.
	Goodrich DE, 2012					FRS (CVD): <10%: 40.7%, 10-20%: 40.7% and >20%: 18.6%
	Goff DC, 2005					FRS (CHD): In men: CATIE study: 9.4 (7.2); NHANES study: 7.0 (6.3) and in women: 6.3 (6.3) and 4.2 (4.5), respectively.
	McCreadie RG, 2003		4.1	9.6		
	Nurjono M, 2014					FRS (CVD): Participants in the highest quartile of serum BDNF had a 3.3 times increased in FRS over those in the lowest quartile.
	Said MA, 2012			6.3 (5.6)		31.5% of patients in the metabolic syndrome group had a high/very high FRS (CHD) vs. 11% in non-metabolic syndrome group (p<0.001)
	Tay YH, 2013	4.7 (4.7)				
	Protopopova D, 2012					SCORE ≥ 5%: 10%
	Arango C, 2008			6.8 (6.9)	0.9 (1.9)	
	Cohn T, 2004					FRS (MI): 8.9% in males, compared with control subjects (6.3) (p<0.001) and 2.6% females (vs. Control subjects 2.0%) (p=0.180).
	McLean G, 2014					Joint British Societies score: risk levels by age group and gender. Age: major risk with 79% of those with schizophrenia aged 65-74 estimated at high risk compared with only 1.3% of those aged 35-44.
	Ratliff JC, 2013	10.7				
	Stroup TS, 2013			7.3 (5.7)		
	Sicras-Mainar A, 2013	11.9 (5.7)				
SMI	Dickerson FB, 2013					FRS (CVD):13.2 (11.9)/74.(7.2) smoking Yes/No
	Druss BG, 2010					FRS (CHD): 6.9/9.8 for intervention/r control group.
	Foguet-Boreu Q, 2013					FRS REGICOR≥10%: 4.6%. SCORE ≥5%: 5.4%
	Osborn DP, 2006					FRS (CHD): median: 5% (IQR:2-12)
Psychiatric diagnoses	Wysokiński A, 2012	6.4 (7.2)	3.7 (2.8)	5.8 (6.1)		
	Correll CU, 2006					FRS (CHD): 8.29 (0.49)/33(0.52) men/women
	Jin H, 2011					FRS (CHD) increased by 79% in schizophrenia, 72% in posttraumatic stress, 61% in mood disorder.
	Mackin P, 2007	11.3 (12.3)	1.7 (3.2)	9.3 (10.5)		
	Margari F, 2013	8.3 (5.8)				
	Correll CU, 2011			2.5 (4.2)		
	Taylor V, 2010					FRS (CHD) lower for patients at baseline but increased during the follow-up. Women showed an increase risk for CHD over time, and men did not.

Table 4. Cardiovascular risk assessment by diagnostic group

Subgroup analysis was performed in six studies (3 involving schizophrenia, 1 depressive disorder and 2 psychiatric diagnoses in general). Higher CVR was observed in patients with schizophrenia than in those with depressive disorder or general psychiatric diagnosis, with a pooled SMD (95% CI) as follows: 0.63 (0.16, 1.09), 0.03 (-0.48, 0.54), and 0.02 (-0.82, 0.86), respectively (Table 5). The sensitivity analysis omitted one study at a time, showing a pooled SMD ranging from 0.19 to 0.50. Funnel plots did not suggest any publication bias.

	Number of studies	**SMD (95% CI)**	I^2
Diagnosis			
Depressive disorder	1	0.03 (-0.48, 0.54)	0%
Schizophrenia	3	0.63 (0.16, 1.09)	94%
Psychiatric diagnosis	2	0.02 (-0.82, 0.86)	92%
Criteria for diagnosis			
NE	1	0.35 (0.24, 0.45)	84%
DSM IV	5	0.32 (-0.11, 0.75)	94%
Study design			
Observational study	5	0.34 (-0.21, 0.88)	94%
RCT	1	0.35 (0.24, 0.45)	0%
Outcome			
CVD total	4	0.40 (-0.44, 1.02)	95%
CHD	1	0.35 (0.24, 0.45)	0%
Stroke	1	0.03 (-0.48, 0.54)	0%

Table 5. Stratified pooled standardized mean differences for cardiovascular risk assessment

Six studies that included 1,065 people with SMI who had a CVR assessment and 1,567 people without SMI were included in the meta-analysis [23,36,40-42,53]. The total overall CVR between the psychiatric group and control group showed a SMD of 0.35 (95% CI: -0.02 - 0.71, P=0.06) with significantly high heterogeneity (I^2=93%; p<0.001) (Figure 2).

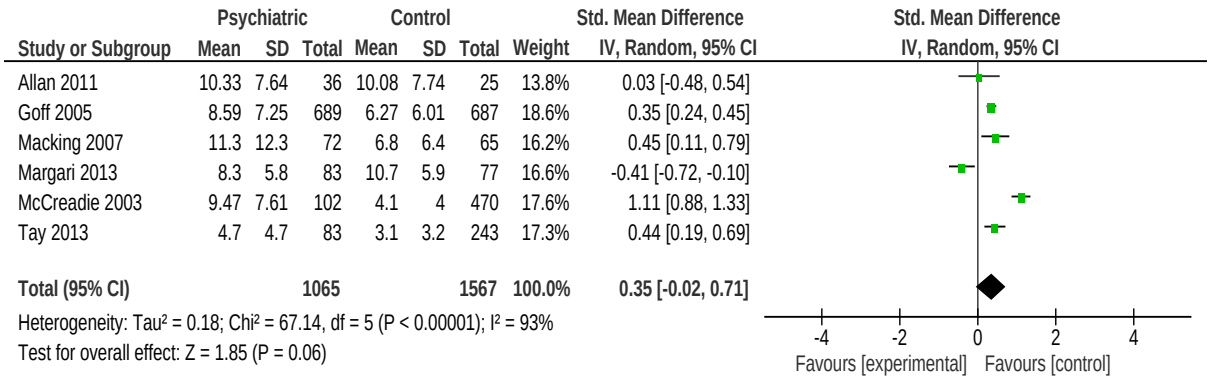


Figure 2. Summary of forest plot. Standardized mean differences between psychiatric group and comparative group

Review: Cardiovascular risk assessment in patients with a severe mental illness

Comparison: Psychiatric versus comparative group

Outcome: Cardiovascular risk assessment

Discussion

Data from studies that reported CVR scores did not support higher risk in patients with SMI than in the control population. Subgroup analysis showed a higher CVR associated with schizophrenia than with other SMIs. Only in patients with schizophrenia was there some evidence of higher CVR scores than in the control population.

To date it has been widely accepted that the prevalence of modifiable risk factors was increased in patients with SMI [57]. Nonetheless, several authors have suggested that not all risk factors were equally increased in these patients. A number of studies have found that smoking and diabetes rates were higher in the SMI population than in the reference population [58], while others observed that hypertension was not increased among SMI patients [33, 58, 59]. Conversely, other authors did not detect significant differences in CVR factors between participants with and without SMI [60]. This could be the result of publication bias affecting CVR studies and therefore affecting CVR assessment. Chapman et al, in a meta-analysis of 42 studies on smoking in patients with schizophrenia, revealed

that studies reporting low prevalence of this risk factor are cited less often than those reporting higher prevalence in this population [61].

Numerous previous studies have noted the importance of CVR factors in patients with SMI, but only a few of them incorporated CVR evaluation in the last 12 years. No other systematic review has been found in the literature on this topic. However, Osborn et al, in a systematic review which objective was to determine the relative risk of some CVR factors in people with SMIs, synthesized data about some studies that reported 10 year cardiovascular risk scores [58]. One controlled community study, including 74 SMI patients found that excess CVR scores showed that participants with SMI had higher FRS (CHD) than participants without SMI (median 10-year risk: 5% vs. 4%) [45]. Another study, including 84 schizophrenic patients showed a significant increase of CVR only in males based on FRS (CHD) (10.4% vs. 6.4%) [42]. And the last, involves 240 patients schizophrenia and schizoaffective disorders showed also an increased risk based on FRS (MI) score only in male patients compared to controls (8.9% vs. 6.3%) [26]. Our review also showed that schizophrenia is the group that have more evidence of higher CVR than control groups and is consistent with other studies [62,63].

However, the discrepancy between data showing higher CVR in SMI and the CVR assessment obtained in our review raises some questions. The tools to measure CVR that have been validated for general population may not apply to patients with SMI. In this sense, Osborn et al proposed a CVR prediction model for this population [64]. In addition to the usual predictors, this model also included social deprivation, heavy alcohol use, SMI diagnosis, and prescriptions for antidepressants and antipsychotics [64]. Another key point is the influence of the prescribed medications on CVR. There is strong evidence that antipsychotic drugs, and to a more restricted degree antidepressants and mood stabilizers, are associated with an increased risk for several physical diseases, including obesity,

dyslipidaemia, diabetes mellitus and so on [65]. Furthermore, unclear benefits of different kinds of antipsychotics (first vs. second-generation antipsychotics) have been reported [66], despite the superior efficacy and greater treatment persistence attributed to second-generation antipsychotics.

Our analysis showed that schizophrenia is the group at highest risk, in consonance with other studies that showed an increased risk in patients with schizophrenia and depression, compared to other SMIs [65,66]. Of the three studies of schizophrenic patients included in the forest plot summary, McCreadie et al [42] clearly had the highest SMD. This difference may be explained by the inclusion of older patients with a longer history of illness compared to the other two studies [36,53].

Strengths and weaknesses of this review

The major strength of this study is that it is the first review to focus on CVR assessments in patients with SMI. The search identified a large number of studies (67) that showed CVR data. Osborn et al centred their attention on studies of CVR factors and also showed results of CVR assessments provided by 4 studies, three of which included only schizophrenia and related disorders; one study also included non-affective chronic psychotic illness [58].

Our study also has a number of limitations to be taken into account. We only searched a single data source, although this limitation was countered by an extensive manual search (snowball method). Furthermore, a large number of studies had no control group, making it impossible to

include them in the meta-analysis. Of the 7 studies with control groups [23,36,40-42,47,53], only 6 had sufficient data for inclusion in the meta-analysis and the heterogeneity of data synthesis was considerable ($I^2 > 75\%$). Therefore, all the conclusions of the meta-analysis should be considered with caution. The variability of the studies included in the meta-

analysis could be attributed to the ages of the participants, the diagnoses included, and differences in study design.

Implications for future research

Further work is needed to establish whether patients with SMI have increased CVR compared to general population. More information on the type of CVR assessment used would help to establish a greater degree of accuracy on this question. A new risk assessment approach may be needed in future studies in order to include other relevant factors (obesity, psychotropic drugs and social deprivation) [62]. In addition, a discussion is needed to reach consensus on an operational definition of SMI that can be applied for research purposes.

Conclusions

A review of literature reporting CVR assessment in patients with SMI did not find sufficient evidence to determine whether or not there is a higher risk in these patients relative to the reference population. Subgroup analysis showed a higher CVR in patients with schizophrenia compared to those with depressive disorder or a psychiatric diagnosis. Only in patients with schizophrenia was there some evidence of higher CVR scores than in the control population. Instead of the generalized idea that SMI is associated with increased CVR, it is important to consider the complexity of summarizing the data because there is no universal definition of SMI or standard methods to describe CVR in this population. Further work is needed to elucidate whether new CVR charts that incorporate intrinsic determinants (as the effect of psychotropic drugs or social deprivation) should be established for risk assessment in this population.

Ethics and consent to participate

Not Applicable.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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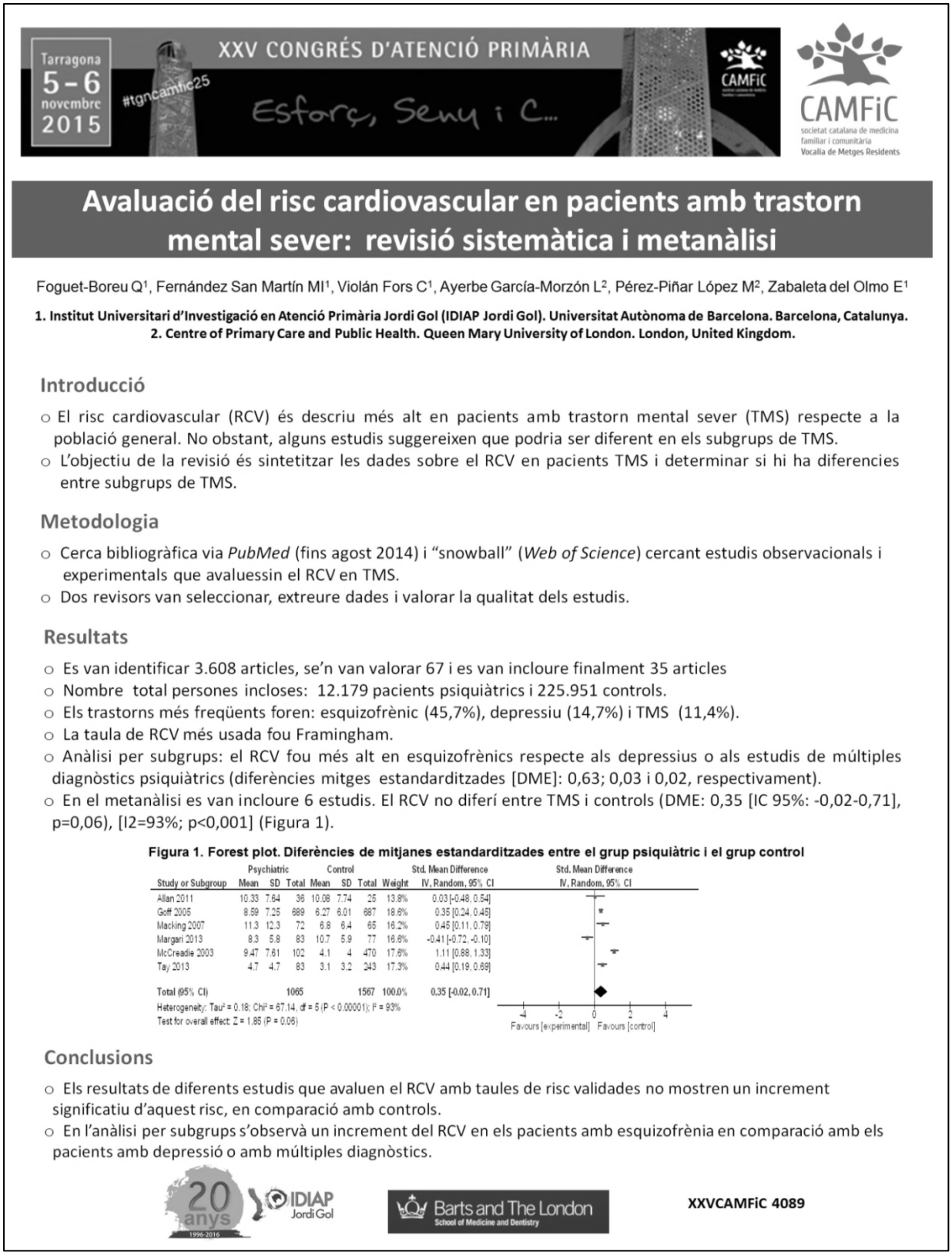

Figura 3.2.1 Poster basado en esta revisión que se presentó en el XXV Congreso de Atención Primaria de la Sociedad Catalana de Medicina Familiar y Comunitaria en Noviembre de 2015

3.3 Preguntas sin respuesta sobre eventos y factores de riesgo cardiovascular en pacientes con patología psiquiátrica

La revisión bibliográfica presentada en este capítulo muestra que la enfermedad psiquiátrica en que se ha estudiado con mayor profundidad el riesgo cardiovascular es la depresión, seguida de la esquizofrenia. La evidencia sobre la asociación con enfermedades y factores de riesgo cardiovascular es mucho más pobre en el caso de los trastornos de ansiedad y la enfermedad bipolar, y marcadamente escasa en el caso de los trastornos de personalidad. Por otro lado la revisión bibliográfica muestra que los mecanismos que explican la mayor incidencia de eventos cardiovasculares en pacientes psiquiátricos siguen sin estar bien descritos. Se ha planteado que las enfermedades mentales pueden producir disfunciones neuroendocrinas, inmunológicas, e inflamatorias que aumentan el riesgo cardiovascular.[27] También, y esto sería de especial relevancia para la atención primaria, muchas enfermedades mentales están asociadas con estilos de vida poco saludables y con una mayor prevalencia de factores de riesgo cardiovascular. [14, 45, 50-54] Sin embargo los estudios que han abordado los factores de riesgo cardiovascular en pacientes con problemas psiquiátricos tienen algunas limitaciones metodológicas, como diseños transversales en muchos casos, y tamaños muéstrales pequenos.[14, 45, 50-54] También se ha sugerido, aunque se ha estudiado de modo superficial, que la asociaciones entre los problemas psiquiátricos y cardiovasculares podrían explicarlas algunos problemas físicos como la diabetes, que es un factor de riesgo para ambas patologías.[27] Por otro lado se ha planteado, aunque la evidencia siga siendo escasa, que la medicación empleada para tratar los problemas psiquiátricos pueda tener un efecto negativo, directo o indirecto sobre la salud cardiovascular.[64-67] El bajo nivel socioeconómico, que se encuentra ligado tanto a los problemas psiquiátricos como cardiovasculares, también podría explicar la asociación de unos con otros.[68-70] Muchos factores asociados a los problemas psiquiátricos, como el deterioro cognitivo, el trato difícil

para el personal sanitario, o el bajo cumplimiento terapéutico, pueden resultar en que estos pacientes reciban una peor calidad de atención, lo que puede llevar a una menor detección y a un peor control de factores de riesgo cardiovascular.[11] Aunque el efecto de las desigualdades de atención sanitaria cuenta también con una evidencia muy escasa.[71]

La historia natural tanto de los problemas psiquiátricos como cardiovasculares puede tener un papel relevante en su asociación, y tampoco ha sido abordada en los estudios disponibles en la literatura. También podría plantearse como hipótesis que los pacientes con problemas de salud mental desarrollen a una edad más precoz problemas cardiovasculares.

3.3.1 Hipótesis planteadas en esta tesis

De acuerdo con la evidencia científica identificadas en la revisión bibliográfica se pueden plantear las siguientes hipótesis, que se probarán en los estudios contenidos en los siguientes capítulos:

- La ansiedad y la depresión se asocian con una mayor incidencia de problemas coronarios e ictus, que es potencialmente explicable en estos pacientes por factores de riesgo cardiovascular, los efectos de la medicación antidepresiva, y el bajo nivel socioeconómico.

-Los eventos cardiovasculares pueden presentarse a una edad más temprana en pacientes con depresión o ansiedad.

- Los pacientes con depresión, ansiedad, esquizofrenia, trastorno bipolar, o trastornos de personalidad, tienen un riesgo elevado de desarrollar factores de riesgo cardiovascular.

- La medicación antidepresiva, antipsicótica, y el bajo nivel socioeconómico, pueden explicar el desarrollo de dichos factores de riesgo cardiovascular en pacientes con problemas psiquiátricos.

- Los factores de riesgo cardiovascular pueden detectarse más tarde en pacientes con enfermedades psiquiátricas

4. EVENTOS CARDIOVASCULARES EN PACIENTES CON DEPRESION Y ANSIEDAD EN ATENCION PRIMARIA

Los problemas afectivos, incluyendo los trastornos ansiosos y depresivos, son la patología psiquiátrica con más impacto en el mundo.[2, 3] El manejo de dichos trastornos recae en muchos casos en sus totalidad sobre el médico de atención primaria, con lo que se consideran especialmente relevantes dentro del área abordada por esta tesis.[37, 72] En la revisión bibliográfica presentada en el capítulo tercero se observó que los mediadores de la asociación entre la depresión, la ansiedad, y la patología cardiovascular no están suficientemente presentes en los estudios disponibles en la literatura.[23-25, 27-29] Por ello se decidió realizar el trabajo que se presenta a continuación, en el que se analiza el riesgo de sufrir un ictus, o un infarto de miocardio en un periodo de diez años en pacientes diagnosticados previamente de depresión o ansiedad. Se estudia también el papel mediador de los factores de riesgo cardiovascular tradicionales, el bajo nivel socioeconómico, y la medicación antidepresiva. Finalmente se compara la edad de presentación de dichos eventos cardiovasculares entre pacientes con depresión o ansiedad y pacientes sin dichos trastornos. Este trabajo ha sido publicado en el *Journal of Affective Disorders*.[73] Un resumen del mismo fue presentado como póster en el *General Adult Psychiatry Faculty Conference* en Londres el 8 de octubre de 2015. Dicho póster se presenta a continuación del artículo completo (Figura 4.1.1).

El el estudio presentado en este capítulo, igual que en el presentado en el capítulo cinco, se emplearon datos de atención primaria de Londres. Esto se debe a que yo trabajo habitualmente en Reino Unido. Las organización del *National Health Service* británico, es muy similar a la de los sistemas de salud españoles. Es un sistema público, con acceso universal, está estructurado en niveles, y todos los pacientes están registrados en un centro

de salud. Por ello los estudios de estos dos capítulos presentan resultados que no serían muy distintos en países con una organización sanitaria similar, concretamente en España, que es donde se presenta esta tesis.

Risk of incident cardiovascular events amongst individuals with anxiety and depression: A prospective cohort study in the east London primary care database

Short Title

Cardiovascular events in individuals with anxiety and depression

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Abstract

Background: It is unknown how risk of myocardial infarction and stroke differ for patients with and without anxiety or depression, and whether this risk can be explained by demographics, medication use, cardiovascular risk factors. The aim of this study is to quantify differences in risk of non-fatal MI or stroke among patients with anxiety or depression.

Methods: Prospective cohort study examining risk of incident MI and stroke between March 2005 and March 2015 for 524,952 patients aged 30 and over from the east London primary care database for patients with anxiety or depression.

Results: Amongst 21,811 individuals with depression at baseline, 1.2% had MI and 0.4% had stroke. Of 22,128 individuals with anxiety at baseline, 1.1% had MI and 0.3% had stroke. Depression was independently associated with both MI and stroke, whereas anxiety was associated with MI only before adjustment for cardiovascular risk factors. Antidepressant use increased risk for MI but not stroke. Mean age at first MI was lower in those with anxiety, while mean age at first stroke was lower in those with depression.

Limitations: The study was limited to patients currently registered in the database and thus we did not have any patients that died during the course of follow-up. Conclusions: Patients with depression have increased risk of cardiovascular events. The finding of no increased cardiovascular risk in those with anxiety after adjusting for cardiovascular risk factors is of clinical importance and highlights that the adequate control of traditional risk factors is the cornerstone of cardiovascular disease prevention. Targeting management of classical cardiovascular risk factors and evaluating the risks of antidepressant prescribing should be prioritized.

Keywords: Depression; anxiety; cardiovascular disease; cohort study; primary care

Introduction

Introduction

The 2010 Global Burden of Disease has identified anxiety and depression as the most prevalent mental health conditions worldwide, contributing significantly to overall global disease burden and years lived with disability.(Ferrari et al., 2013; World Federation For Mental Health, 2012) In the UK, anxiety and depressive disorders affect approximately 15% of the adult population.(LSE and The Centre for Economic Performance, 2012)

Patients with psychiatric conditions have an increased risk of cardiovascular disease (CVD), including myocardial infarction (MI) and stroke.(De Schutter et al., 2011; Elderon and Whooley, 2013; Hare et al., 2014; Osborn et al., 2007; Tully et al., 2015) Both anxiety and depression are common mental disorders, with high prevalence in the general population. While the relationship between severe mental illness and cardiovascular disease has been widely explored, there is a paucity of evidence around the relationship between anxiety and incident cardiovascular events.(Bowen et al., 2000; Chou et al., 2012; Davies and Allgulander, 2013; Lambiase et al., 2014; Osborn et al., 2007) The burden of CVD and CVD risk factors is increasing rapidly amongst young, working-age adults. (Lavie and Milani, 2006; Moran et al., 2014; Poisson et al., 2014) Since cardiovascular disease is the leading cause of loss of in disability adjusted life- years (DALYs) worldwide, this represents the greatest loss for families and national economies. Accordingly, it is important to know whether individuals with anxiety or depressive disorders are at risk of earlier onset of MI and stroke compared to individuals without these conditions.(Murray et al., 2012)

This study aims firstly to quantify the excess risk of non-fatal stroke or MI associated with diagnosed anxiety and depressive disorders and antidepressant use in an unselected primary care population, and secondly, to test the hypothesis that cardiovascular (CV) events may have an earlier presentation in patients with anxiety and depressive disorders compared to those without. We hypothesize that risk will be increased in patients

with these psychiatric conditions compared to those without and that the increased risk can be further explained by sociodemographic and cardiovascular risk factors. This work will help to identify groups at higher risk for cardiovascular outcomes and potential areas for focusing preventive interventions.

Methods

A prospective cohort study using patients contributing to the east London primary care database held by the Clinical Effectiveness Group at Queen Mary, University of London was undertaken. The database comprises the electronic health records of approximately 950,000 individuals registered with 141 general practices across the east London boroughs of Tower Hamlets, Newham, and City & Hackney, all of which use EMIS web as their clinical computer system. The population of east London is one of the most deprived in the UK and has high levels of ethnic diversity, with over 50% of the resident population of non-white ethnicity.(Hull et al., 2014; Tower Hamlets Council, 2013)

The study sample included all adult patients aged 30 and over in March 2015 who were free from MI or stroke at the start of the study period. Anonymised demographic, clinical and prescribing data were extracted for all individuals meeting the study entry criteria.

Read codes are the standard clinical terminology system used in general practice across the UK.(Chisholm, 1990) Diagnostic Read codes for anxiety and depressive disorders were selected by the authors, who comprised general practitioners, clinical psychiatrists, and epidemiologists (Supplement 1). Diagnoses of diabetes mellitus, before March 2005, and MI and stroke, between March 2005 and March 2015, were defined according the quality and outcomes framework Read code specifications.(NHS Employers, 2014) Individuals without a diagnostic Read code for each condition were considered to be free from the disease of interest.

Self-reported ethnicity was recorded at the practice during registration or routine consultation. Ethnic categories were based on the UK census and for this study were condensed into four categories: White (British, Irish, other white), Black (Black African, Black Caribbean, other Black) South Asian (Bangladeshi, Pakistani, Indian, other South Asian) and any other ethnic group. Patients with mixed ethnicity were grouped with their parent ethnic minority. Individuals with missing ethnicity information were grouped into an "unknown" category (results not shown). Deprivation was classified using the Townsend deprivation score, a census-based index of material deprivation calculated by the combination of four variables from the 2001 census: car ownership, overcrowded households, households not owner occupied, and unemployment.(Townsend, 1987)

Systolic and diastolic blood pressure, total cholesterol level, tobacco consumption and antidepressant use closest to and before March 2005 were extracted to identify baseline values at study entry. Hypertension was identified using the clinical Read code for hypertensive disease. Obesity was defined as having a body mass index of 30 kg/m2 or above; Hyperlipidemia was defined as having a total cholesterol value of greater than 5 mmol/L; Tobacco consumption was dichotomized into current smoker vs. not current smoker. Individuals without Read codes for tobacco consumption were considered to be non-current smokers.

Individuals entered the study in March 2005 and were followed up until they experienced an incident non-fatal event of MI or stroke during the ten years of follow-up. Follow-up time was censored at the end of the study period in March 2015 if they did not experience the outcome of interest.

Cox proportional-hazards regression analyses were used to firstly compare the risk of incident MI and stroke in patients with and without depression at baseline and secondly to compare the risk of incident MI and stroke in patient with and without anxiety at baseline….

Three regression models were built; The first adjusted for age, gender, and ethnic group, the second additionally adjusted for diabetes, hypertension, hyperlipidemia, and smoking antidepressant prescribing at baseline, obesity, and Townsend deprivation score, and the third additionally adjusted for the presence of co-morbid anxiety or depression. Linear regression models adjusting for gender and ethnicity were used to compare the age at the time of MI and stroke of patients with and without anxiety and depression. All models accounted for clustering of patients within general practices using a shared frailty term for practice, which reflects the non-independence of patients attending the same health care provider.(Allison, 2014)

Results

A total of 524,952 adults aged 30 and over registered with the east London primary care database in March 2015 were identified. The characteristics of the study sample are presented in table 1. From the total population, 21,811 individuals had an existing diagnosis of depression at baseline (4.1%) while 22,128 had an existing diagnosis of anxiety (4.2%). Compared to individuals free from psychiatric disorders, individuals with depression or anxiety were older, had a higher proportion of females and a smaller proportion of individuals from ethnic minority groups ($p<0.001$). Prevalence of all clinical co-morbidities at baseline was higher in those with anxiety or depressive disorders, most notably hyperlipidemia was present in 60% of those with anxiety or depressive disorders and 40% of those without anxiety or depressive disorders ($p<0.001$). Similarly, 40% of those with anxiety or depressive disorders were identified as current smokers, compared to 27% of the general population. Incidence of both MI and stroke was doubled for those with anxiety or depressive disorders compared to those without ($p<0.001$).

	Whole cohort n (%)	Anxiety n (%)	Non-Anxiety n (%)	p	Depression n (%)	Non-Depression n (%)	p
N	524,952 (100)	22,128 (4.2)	502,824 (95.8)		21,811 (4.1)	503,141 (95.9)	
Demographic characteristics at baseline							
Mean age (SD)	35.9 (13.9)	42.7 (13.9)	35.6 (13.8)	<0.001	43.2 (13.5)	35.6 (13.8)	<0.001
Median age (IQR)	32 (25-44)	41 (32-52)	32 (24-43)		42 (33-52)	32 (24-43)	
Female	247,528 (47.1)	13,267 (60.0)	234,261 (46.6)	<0.001	13,777 (63.2)	233,751 (46.5)	<0.001
Male	277,423 (52.8)	8,861 (40.0)	268,562 (53.4)		8034 (36.8)	269,389 (53.5)	
White	220,079 (41.9)	13,863 (62.6)	206,216 (41.0)	<0.001	13,436 (61.6)	206,643 (41.1)	<0.001
South Asian	144,666 (25.6)	3,507 (15.8)	141,159 (28.1)		3,182 (14.6)	141,484 (28.1)	
Black	89,186 (17.0)	2,739 (12.4)	86,447 (17.2)		3,155 (14.5)	86,031 (17.1)	
Other	32,425 (6.2)	889 (4.0)	31,536 (6.3)		869 (4.0)	31,556 (6.3)	
Unknown	38,596 (7.4)	1,130 (5.1)	37,466 (7.5)		1,169 (5.4)	37,427 (7.4)	
Mean Townsend score (SD)	5.2 (1.8)	5.4 (1.8)	5.2 (1.8)	<0.001	5.5 (1.7)	5.2 (1.8)	<0.001
Prevalent cardiovascular risk factors and medication use at baseline							
Diabetes mellitus	50,081 (9.5)	2,804 (12.7)	47,277 (9.4)	<0.001	3,098 (14.20)	46,983 (9.3)	<0.001
Current smoker	145,862 (27.8)	8,378 (37.9)	137,484 (27.3)	<0.001	8,897 (40.8)	136,965 (27.2)	<0.001
Hypertension	86,946 (16.6)	5,829 (26.3)	81,117(16.1)	<0.001	5,613 (25.7)	81,333 (16.2)	<0.001
Hyperlipidemia (≥5 mmol/L)	204,682 (40.0)	13,223 (59.8)	191,459 (38.1)	<0.001	13,392 (61.4)	191,290 (38.0)	<0.001
Antidepressant use	125,532 (23.9)	15,228 (68.8)	110,304 (21.9)	<0.001	16,659 (76.4)	108,873 (21.6)	<0.001
Obesity (≥30 kg/m^2)	36,195 (6.9)	3,417 (15.4)	32,778 (6.5)	<0.001	3,791 (17.4)	32,404 (6.4)	<0.001
Anxiety		--	--		5,132 (23.5)	16,996 (3.4)	<0.001
Depression		5,132 (23.2)	16,679 (3.3)	<0.001	--	--	
Incident CVD 2005-2015							
Incident MI	3,390 (0.7)	247 (1.1)	3,143 (0.6)	<0.001	263 (1.2)	21,327 (0.6)	<0.001
Mean age at first MI (SD)	59.5 (13.4)	58.5 (11.2)			61.2 (12.9)		
Incident Stroke	987 (0.2)	68 (0.3)	919 (0.2)	<0.001	79 (0.4)	908 (0.2)	<0.001
Mean age at first Stroke (SD)	61.6 (15.3)	63.4 (12.7)			59.2 (13.0)		

Table 1. Description of study sample *Comparisons between patients with/without anxiety and with/without depression were made using t-tests for continuous variables, and from chi-squared test for unordered categorical variables

As all included patients were necessarily registered in the database in March 2015, all were able to contribute a full ten years of follow-up time to the study. Cumulative-hazard curves illustrating the increased cumulative incidence of MI and Stroke in individuals with anxiety or depression compared to those without are shown in figure 1.

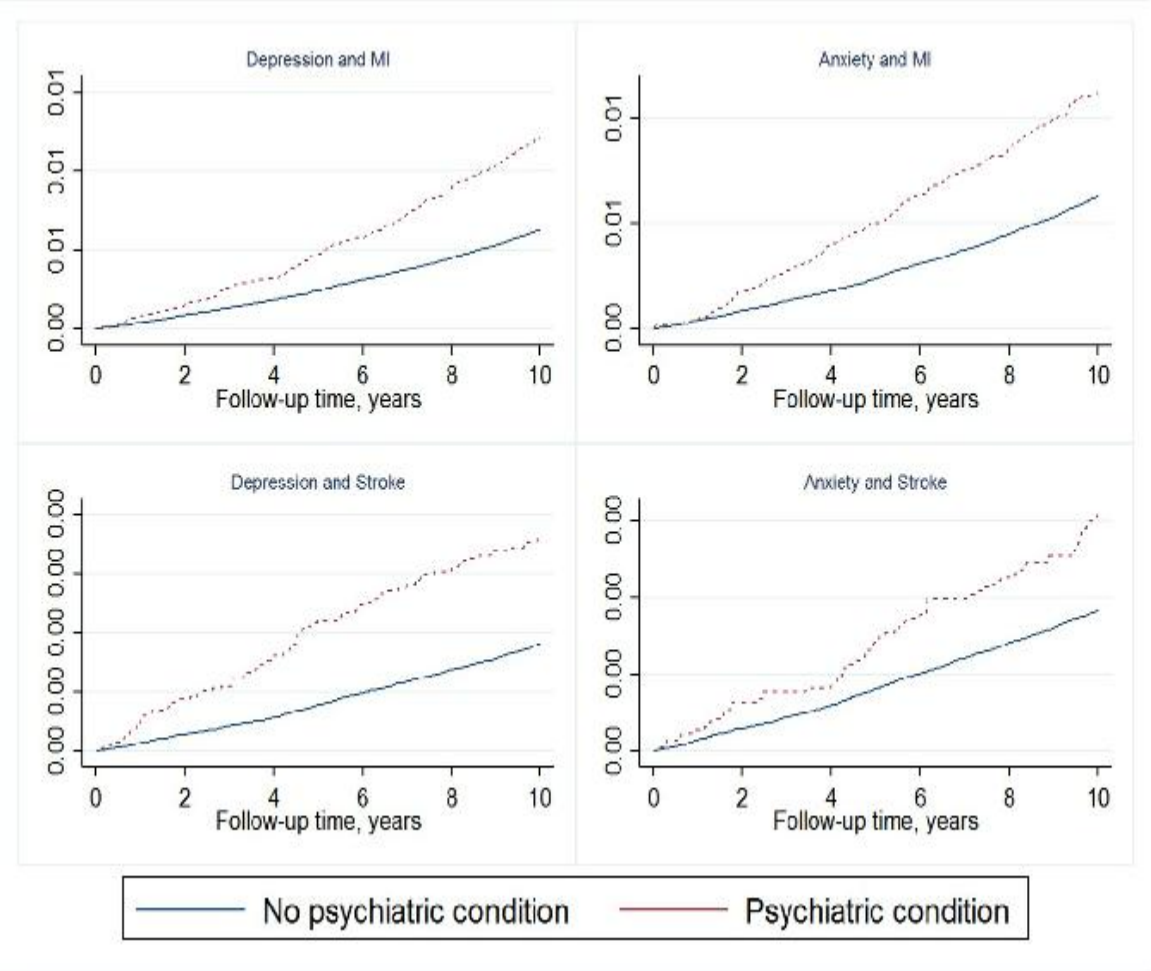

Figure 1. Cumulative Hazard Curves for incidence of MI and Stroke in patients with Anxiety or Depression

Cox proportional hazards models for the risk of incident non-fatal MI and stroke for patients with and without anxiety are presented in table 2. After adjusting for age, gender, and ethnic group (model 1), the risk of MI was raised by 33% in those with anxiety relative to those without (HR 1.33, CI95% 1.17, 1.52). After adjustment for baseline risk factors and

deprivation in model 2, the association between anxiety and MI was attenuated, and association did not reach the level of statistical significance (HR 1.10, CI95% 0.96, 1.26). This lack of association remained after, adjustment for co-morbid depression in model 3 (HR 1.08, CI95% 0.94, 1.24). An independent association between antidepressants and MI was observed in the analysis for anxiety (HR 1.25, CI95% 1.13, 1.39). No evidence for a relationship between anxiety and stroke was evident in any of the survival analysis models (Table 2).

	Risk of MI			Risk of Stroke		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Anxiety at baseline	1.33*** (1.17-1.52)	1.10 (0.96-1.26)	1.08 (0.94-1.24)	1.17 (0.91-1.51)	1.09 (0.84-1.41)	1.06 (0.81-1.38)
Age	1.07*** (1.07-1.08)	1.07*** (1.07-1.07)	1.07*** (1.07-1.07)	1.08*** (1.07-1.08)	1.07*** (1.07-1.08)	1.07*** (1.07-1.08)
Gender						
Female	1 --	1 --	1	1	1	1
Male	2.87*** (2.66-3.10)	2.82*** (2.61-3.05)	2.84*** (2.62-3.06)	1.43*** (1.26-1.62)	1.43*** (1.26-1.63)	1.44*** (1.26-1.63)
Ethnic Group						
White	1	1	1	1	1	1
South Asian	1.86*** (1.71-2.02)	1.86*** (1.71-2.03)	1.87*** (1.72-2.04)	1.24* (1.04-1.48)	1.18 (0.99-1.42)	1.19 (1.00-1.43)
Black African/Caribbean	0.52*** (0.46-0.59)	0.51*** (0.45-0.57)	0.51*** (0.45-0.58)	1.40*** (1.19-1.65)	1.29** (1.09-1.52)	1.29** (1.09-1.53)
Other ethnic group	0.76** (0.63-0.92)	0.81* (0.68-0.98)	0.82* (0.68-0.99)	1.09 (0.80-1.49)	1.10 (0.80-1.50)	1.10 (0.81-1.51)
Hypertension		1.17*** (1.07-1.28)	1.17*** (1.07-1.28)		1.47*** (1.25-1.73)	1.47*** (1.25-1.73)
Diabetes Mellitus		1.48*** (1.33-1.63)	1.48*** (1.33-1.63)		1.46*** (1.21-1.75)	1.46*** (1.21-1.75)
Hyperlipidemia		1.12* (1.02-1.22)	1.12* (1.02-1.22)		0.89 (0.75,1.05)	0.89 (0.75-1.05)
Current smoker		2.03*** (1.87-2.20)	2.02*** (1.86-2.19)		1.33** (1.12-1.59)	1.33** (1.11-1.58)
Antidepressant use		1.25*** (1.13-1.39)	1.20*** (1.08-1.34)		1.07 (0.87-1.30)	1.01 (0.82-1.24)
Townsend deprivation score		1.06*** (1.04,1.09)	1.06*** (1.04,1.08)		1.03 (0.99-1.07)	1.03 (0.99-1.07)
Obesity		1.73*** (1.60,1.87)	1.73*** (1.60-1.87)		1.45*** (1.25-1.68)	1.45*** (1.25-1.68)
Depression			1.21** (1.05-1.39)			1.29 (1.00-1.66)

Table 2. Association between anxiety and MI/Stroke (n=524,916)* Columns display hazard ratio, and 95% confidence interval, *p<0.05 **p<0.01 ***p<0.0001, all models account for clustering by general practice

Cox proportional hazards models for the risk of incident non-fatal MI and stroke for patients with and without depressive disorders are presented in table 3. After adjusting for age, gender, and ethnic group in model 1, the risk of MI was raised by 52% in those with depressive disorders compared to those without (HR 1.52 CI95% 1.34, 1.73). The risk of stroke was raised by 43% in those with depressive disorders compared to those without after adjusting for the same (HR 1.43 CI95% 1.11, 1.78). The independent effect of depressive disorders on risk of incident MI and stroke remained after additionally adjusting for cardiovascular risk factors, medication use, and deprivation in model 2 (MI HR 1.22, CI95% 1.06, 1.40, Stroke HR 1.29, CI95% 1.00-1.67). Finally, adjusting for the presence of anxiety at baseline in model 3 did not have an appreciable effect on the independent effect of depressive disorders on MI and stroke. As with the previous analysis, independent associations between antidepressants and MI were also observed in the analysis for depression.

	Risk of MI			Risk of Stroke		
	Model 1	Model 2	Model 3	Model1	Model2	Model 3
Depression at baseline	1.52*** (1.34-1.73)	1.22*** (1.06-1.40)	1.21** (1.05-1.39)	1.40** (1.11-1.78)	1.29* (1.00-1.67)	1.29 (1.00-1.66)
Age	1.07*** (1.07-1.08)	1.07*** (1.07-1.07)	1.07*** (1.07-1.07)	1.08*** (1.07-1.08)	1.07*** (1.07-1.08)	1.07*** (1.07-1.08)
Gender						
Female	1	1	1	1	1	1
Male	2.89*** (2.68-3.12)	2.83*** (2.62-3.06)	2.84*** (2.62-3.06)	1.44*** (1.27-1.63)	1.43*** (1.26-1.63)	1.44*** (1.26-1.63)
Ethnic Group						
White	1	1	1	1	1	1
South Asian	1.87*** (1.72-2.03)	1.87*** (1.72-2.04)	1.87*** (1.72-2.04)	1.25* (1.05-1.49)	1.19 (1.00-1.43)	1.19 (1.00-1.43)
Black African/Caribbean	0.52*** (0.46-0.59)	0.51*** (0.45-0.58)	0.51*** (0.45-0.58)	1.41*** (1.20-1.66)	1.29** (1.09-1.53)	1.29** (1.09-1.53)
Other ethnic group	0.77** (0.64-0.92)	0.82* (0.68-0.98)	0.82* (0.68-0.99)	1.10 (0.80-1.50)	1.10 (0.81-1.51)	1.10 (0.81-1.51)
Hypertension		1.17*** (1.07-1.28)	1.17*** (1.07-1.28)		1.47*** (1.25-1.73)	1.47*** (1.25-1.73)
Diabetes Mellitus		1.47*** (1.33-1.63)	1.48*** (1.33-1.63)		1.45*** (1.21-1.75)	1.46*** (1.21-1.75)
Hyperlipidemia		1.12* (1.02-1.22)	1.12* (1.02-1.22)		0.89 (0.75-1.05)	0.89 (0.75-1.05)
Current smoker		2.02*** (1.86-2.19)	2.02*** (1.86-2.19)		1.33** (1.12-1.58)	1.33** (1.11-1.58
Antidepressant use		1.22*** (1.10-1.35)	1.20*** (1.08-1.34)		1.02 (0.83-1.25)	1.01 (0.82-1.24)
Townsend deprivation score		1.06*** (1.04-1.08)	1.06*** (1.04-1.08)		1.03 (0.99-1.07)	1.03 (0.99-1.07)
Obesity		1.73*** (1.60-1.87)	1.73*** (1.60-1.87)		1.45*** (1.25-1.68)	1.45*** (1.25-1.68)
Anxiety			1.08 (0.94-1.24)		(1.25-1.68)	1.06 (0.81-1.38)

Table 3. Association between depressive disorders and MI/Stroke (n=524,916)

* Columns display hazard ratio, and 95% confidence interval, *p<0.05 **p<0.01 ***p<0.0001, all models account for clustering by general practice.

Multivariable analyses examining differences in age at first CVD presentation according to psychiatric condition showed that anxiety was associated with an earlier presentation of MI 3.6 years (2.1-5.0) p<0.001 and depression was associated with an earlier presentation of

strokes 4.1 years (1.1-7.1) p=0.008. There were no significant associations between depression and age at time of MI, or anxiety and age at the time of stroke (Table 4).

	Difference in age at presentation (years)		
MI	Coefficient	CI95%	p
Anxiety	-3.6	-5.0– -2.1	<0.001
Depression	-1.0	-2.5– 0.5	0.203
Stroke			
Anxiety	0.5	-2.7– 3.7	0.736
Depression	-4.1	-7.1 – -1.1	0.008

Table 4. Age at first presentation of MI and Stroke

Discussion

Principal Findings

This study has used a large electronic health database to highlight the heterogeneity of risk of cardiovascular outcomes according to psychiatric disorder in an ethnically and socially diverse population. While the study demonstrates a strong relationship between depression and cardiovascular disease, the evidence for a relationship between cardiovascular disease and anxiety is weaker. The study shows that the mean age at first MI is lower in those with anxiety, while mean age at first stroke is lower in those with depression. Furthermore, the study has shown a strong independent effect of antidepressant on risk of MI, but not stroke. Our findings show that traditional cardiovascular risk factors can explain part of the association between anxiety, depression and cardiovascular disease. This is encouraging as the majority of these modifiable risk factors can be managed in primary care. The association between anxiety and incident MI was reduced after adjustment for cardiovascular risk factors. Traditional cardiovascular risk factors and antidepressant use accounted for a greater amount of the association between depression and MI, as evidenced by the risk associated with depressive disorders decreasing from 52% to 21% after full adjustment, and a smaller proportion of the association between depression and stroke (reduction in risk associated with depressive disorders from 40% to 29%).

Comparisons with existing literature

The associations between depressive disorders/anxiety and MI, and between depressive disorders and stroke confirm those of previous studies.(Dong et al.,2012; Pan et al., 2014; Roest et al., 2010; Van der Kooy et al., 2007) While strong evidence for a relationship between anxiety and fatal myocardial has been found, the evidence for a relationship with non-fatal MI is more equivocal.(Roest et al., 2010). Anxiety has been shown to increase risk of incident stroke in recent studies in a US setting.(Lambiase et al., 2014; Thurston et al., 2013) The lack of a relationship in our study may be due to lack of reliable assessment of anxiety, or the fact that we did not capture fatal events, and may have thus underestimated the relationship between anxiety and incident CVD.

The finding of increased cardiovascular risk amongst people with diagnosed depression reinforces that of recent studies: A 2014 meta-analysis of 28 cohort studies (n= 681,139) examining the risk of incident stroke in patients with depression reported a pooled estimate of 1.40 (CI95% 1.27-1.53) which aligns closely with the findings reported in above.(Barlinn and Kepplinger, 2015) Of the 28 studies, two were based in the UK; the first reported no relationship between stroke and depression or anxiety, while the second reported a relationship between depression and coronary heart disease, but not stroke. (Surtees et al., 2008)(Brunner et al., 2014)

Associations with antidepressant prescribing

The independent association between antidepressants and cardiovascular outcomes has been demonstrated before.(Pan et al., 2014) Clinical prescribing in general practice is largely guided by evidence from randomized control trials, which tend to be conducted in idealized populations and have a short duration. In the absence of RCTs, the long term observation and follow-up of patients via routine electronic health databases will provide the timeliest

evidence around the benefits and risks of medication use in the general population.(Ayerbe et al., 2014; Coupland et al., 2011) While we cannot infer causality from our observations, our results add to a significant body of evidence suggesting that antidepressants should be prescribed, balancing the benefits with the negative side effects associated with them in the long term.

Strengths

Clinical data on anxiety and depression have been widely used for research purposes since large electronic databases have become available. Electronic health databases provide a platform to conduct high resolution research on very specific and clinically meaningful outcomes that are difficult to investigate with smaller cohorts. (Daskalopolou et al., 2016; Chou et al., 2012).The east London database covers a large, unselected, and geographically contiguous population, allowing for the capture of sufficient numbers of patients with the two most common psychiatric conditions to explore the relationship with cardiovascular outcomes. Given that 99% of the UK population is registered with a general practitioner, we are likely to have captured an accurate cross-section of the population of east London. The findings of this study can be generalized to other primary care populations in urban settings with high ethnic and social diversity.

The east London database captures all prescriptions issued by the general practice team. Though the database does not provide information on whether the prescriptions are filled, a comparison of prescribing data from electronic health databases and NHS dispensing data shows the two sources to be highly comparable, with 97% of cardiovascular medications dispensed as prescribed. (The NHS Information Centre, 2011) The prospective nature of this study ensured that we captured incident cardiovascular events recorded after the onset of depression or anxiety, limiting the possibility of reverse causality. All data were entered into

the medical record prospectively, minimizing the risk of recall bias or inaccurate self-report. The study accounted for the presence of well-established risk factors for cardiovascular disease and benefitted from high levels of ethnicity recording and patient level deprivation data, which allowed for a more accurate estimation of the independent effect of anxiety and depressive disorders on the CVD outcomes. This study has demonstrated that it is possible to replicate and confirm results from non-observational studies and trials in an electronic health database setting using observational epidemiology methodology.

The capture and coding of both anxiety and depressive disorders is clearly outlined in the UK National Institute for Health and Care Excellence guidelines, and thus we expect that general practitioners will code this information consistently and to a high level. (NICE, 2014; NICE, 2011) Furthermore, incentive payments for the accurate recording of depression as part of the Quality and Outcomes Framework were introduced in 2006. A systematic review of the validity of diagnoses in the General Practice Research Database, which collects data identical to that used in our study has shown that 83% of cases with mental and behavioural disorders present in the GPRD were confirmed by general practitioners. (Herrett et al., 2010)

Limitations

Anxiety and depressive disorders tend to be under-diagnosed in primary care settings. (Rait et al., 2009; Robert et al., 1997; Stein and Sareen, 2015) Furthermore, lower rates of healthcare usage amongst patients with these conditions may limit the opportunity to recognize major cardiovascular conditions in these populations.(Yeomans et al., 2014). The over diagnosis of depressive disorders, coupled with the under diagnosis of those who have depressive disorders but don't seek medical help due to reduced motivation, may lead to an underestimation of the associations between depressive disorders and cardiovascular

disease. (Mitchell et al., 2009) As a result, this study may have had reduced power to detect the true relationship between anxiety and depressive disorders and subsequent cardiovascular events. Furthermore, due to the nature of the data, we were unable to assess disease stage (for example, current, remitted, mild, moderate, severe), which could have an impact on the risk of incident cardiovascular disease. Data on physical activity were only available for 27.6% of the study sample and therefore adjustment for this confounder was not possible.

The study included all patients currently registered in the database in 2015 and thus we did not have any patients that died during the course of follow-up. Lack of linkage to hospital episode statistics or mortality data meant that we were unable to examine all-cause mortality or CV related mortality in the study population. Furthermore we were unable to determine whether any hospital admissions for MI or stroke had occurred prior to study entry, and thus we had to assume that the first recorded event in the primary care database was truly incident.

Though our study accounted for ever use of antidepressants, it did not take consider the dosage, drug type, or continuity of prescribing. The study also did not consider antipsychotic medication which has been shown to increase risk of stroke, but not MI. (Brauer et al., 2011; Douglas and Smeeth, 2008)

We examined incidence of cardiovascular outcomes over the previous 10 years; this was due to confidence in the quality of the recorded covariate and diagnostic data following the introduction of the Quality and Outcomes Framework in 2004, which rewarded general practices for high quality and complete recording of priority clinical conditions and risk factors across the UK.(NHS Employers, 2014)

We were unable to examine a “disease-free” cohort and follow them up prospectively to compare CVD outcomes between patients who developed anxiety/depression and those who

did not. Furthermore, our use of baseline measures of key cardiovascular risk factors did not fully account for the time varying nature of risk factor control, which can change in response to both pharmacological and non-pharmacological intervention by the clinician, and in response to changes in morbidity status of the patient.

Unanswered questions and future research

Coded diagnoses for anxiety and depressive disorders do not provide any information as to the severity of the condition, which is likely to affect subsequent healthcare usage and cardiovascular risk. Using additional information to refine the classification of disease severity would improve the estimation of the independent effect of anxiety and depressive disorders on subsequent cardiovascular outcomes.(Kubzansky et al., 1998)

Small numbers of patients with diagnosed psychiatric conditions other than anxiety and depressive disorders meant that we were unable to extend the same analysis to other relevant conditions such as those with schizophrenia, bipolar disorder, or personality disorders, which have been found to have a significant relationship with cardiovascular outcomes.(Ringen et al., 2014) For the same reason, we were unable to estimate CV risk in individuals with more than one prevalent psychiatric condition at baseline. Conducting the analysis in larger or multiple electronic health databases would allow for the study of a wider range of psychiatric disorders would be valuable in confirming or refuting the findings, and also exploring risk in patients with concurrent anxiety and depressive disorders.

Clinical Relevance

In conclusion, the evidence provided in this paper contributes to a better understanding of the association between anxiety and CVD, which has received little attention and confirms

existing literature around the relationship between depression and MI/stroke. The weaker relationship between anxiety and excess risk of MI (after adjustment for traditional cardiovascular risk factors) is of clinical importance and highlights that control of traditional risk factors is the cornerstone of cardiovascular disease prevention, even in populations with psychiatric disorders. Our findings suggest that strict control of cardiovascular risk factors among patients with anxiety disorders may reduce the risk of coronary or cerebrovascular events to a level equivalent to that for patients without anxiety. Our findings for depressive disorders suggest an independent effect of depression which persists despite accounting for cardiovascular risk factor control. Targeting more intensive management of cardiovascular risk factors and evaluating the benefit risk ratio of antidepressant prescribing should be prioritized amongst primary care teams.

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Highlights

• The study finds strong evidence for an independent association between depression and cardiovascular events, and weaker evidence for an association with anxiety.

• Mean age at first MI is lower in those with anxiety compared to those without anxiety, while mean age at first stroke is lower in those with depression compared to those without depression.

• The study shows an independent effect of antidepressant prescribing on risk of MI, but not stroke.

• The findings highlight that that control of traditional risk factors is the cornerstone of cardiovascular disease prevention in populations with psychiatric conditions.

• Targeting intensive management of classical cardiovascular risk factors and evaluating the benefit risk ratio of antidepressant prescribing should be prioritized amongst primary care teams.

Conflict of interests: none

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Data sharing statement

The data used for this study are drawn from the anonymised clinical records of patients in the east London Database and are not available for sharing.

Supplement 1. Read codes used to define Depression or Anxiety

Depression: Read Term	Freq.	Anxiety: Read Term	Freq.
CONSULTATION:Depression	1	AGORAPHOBIA	1
Chronic depression	1,522	ANXIETY REACTION	1
DEPRESSION	41	ANXIETY STATE	1
Depressed Mood	1	Acrophobia	2
Depression	5,085	Acute Anxiety State	16
Depression NOS	1,163	Agoraphobia	90
Depression NOS tearful and low mood pre	1	Agoraphobia - no panic attacks	1
Depressive disorder	6	Agoraphobia - no panic attacks (GMS)	1
Depressive disorder NEC	7,132	Agoraphobia with panic attacks	290
Mild depression	31	Agoraphobia without mention of panic att	24
Mild depression (GMS)	2	Animal phobia	39
Moderate depression	54	Anxiety & Depression	4
Moderate major depression	1	Anxiety State	3
Postviral depression	8	Anxiety Symptoms	197
Premenstrual dysphoric disorder	8	Anxiety Symptoms Related To Bomb	12
Query Depressive disorder NEC	1	Anxiety disorder	4
Query [X]Moderate depressive episode	1	Anxiety state	2,676
Recurrent major depressive episodes, sev	186	Anxiety state NOS	2,321
Severe depression	40	Anxiety state unspecified	647
Single major depressive episode, severe,	2	Anxiety states	14,274
[X] Reactive depression NOS	1,288	Anxiety with depression	18,338
[X]Antenatal depression	1	Cancer phobia	68
[X]Atypical depression	8	Chronic Anxiety State	9
[X]Depression NOS	17,170	Chronic anxiety	799
[X]Depressive disorder NOS	111	Claustrophobia	401
[X]Depressive episode	1,910	Dental phobia	69
[X]Depressive episode, unspecf	15	Fear of crowds	2
[X]Depressive episode, unspecf (GMS)	184	Fear of death	9
[X]Depressive episode, unspecified	1,226	Fear of flying	1,241
[X]Endogen depress no psychot	4	Fear of pregnancy	36
[X]Endogen depress+psychot	1	Flying Fear /Ox	1
[X]Endogenous depression with psychotic	21	Generalised anxiety disorder	812
[X]Endogenous depression without psychot	3	Mixed anxiety and depressive disorder	30
[X]Major depression, mild	3	Mixed anxiety and depressive disorder (G	4

[X]Major depression, moderately severe	36	Needle Phobia	1
[X]Major depression, recurrent without p	5	Other Phobias	12
[X]Major depression, severe with psychot	47	Other phobias	58
[X]Major depression, severe without psyc	15	PANIC ATTACK (S)	2
[X]Manic-dep,depress+psychotic	1	PANIC ATTACK(S)	7
[X]Manic-depress psychosis,depressd,no p	1	PHOBIA	1
[X]Manic-depress psychosis,depressed typ	2	Panic Attacks	27
[X]Mild depression	409	Panic Disorder	2
[X]Mild depressive episode	1,736	Panic attack	6,058
[X]Moderate depressive episode	4,195	Panic disorder	1,219
[X]Moderate depressve episode (GMS)	18	Panic disorder without agoraphobia	2
[X]Monopolar depression NOS	1	Phobia unspecified	170
[X]Other depressive episodes	34	Phobic Anxiety	33
[X]Other recurrent depressive disorders	7	Phobic State	1
[X]Prolonged single episode of reactive	6	Phobic anxiety	303
[X]Rec psychogen dep psychosis	1	Phobic disorder NOS	24
[X]Recur epis/psychogen depres	1	Phobic disorders	41
[X]Recur epis/react depression	1	Phobic state	3
[X]Recur,major dep+psychotic	1	Query Generalised anxiety disorder	1
[X]Recurr dep now sever+psych	1	Query Panic attack	3
[X]Recurr dep now sever+psych (GMS)	2	Query Panic disorder	1
[X]Recurr depress disorder cur epi sever	6	Recurrent anxiety	331
[X]Recurr major depr ep, severe with psy	45	School Phobia	1
[X]Recurr severe episodes/major depressi	4	Social phobia (GMS)	1
[X]Recurrent depress disorder cur epi se	10	Social phobia, fear of public speaking	29
[X]Recurrent depressive disord (GMS)	4	Social phobia-eating in public (GMS)	1
[X]Recurrent depressive disorder	504	Social phobic disorders	62
[X]Recurrent depressive disorder, curren	10	Stress - acute reaction	2
[X]Recurrent depressive disorder, curren	19	Test request: Anxiety with depression	1
[X]Recurrent depressive disorder, curren	10	Weight fixation	3
[X]Recurrent depressive disorder, unspec	26	[X]Agoraphob no hist/panic dis	21

[X]Recurrent episodes of depressive reac	1	[X]Agoraphobia	273
[X]Recurrent episodes of psychogenic dep	3	[X]Agrophob no hist/panic dis	3
[X]Recurrent episodes of reactive depres	4	[X]Animal phobias	5
[X]Recurrent psychotic depress	30	[X]Anxiety NOS	2,742
[X]Recurrent severe episodes of psychoti	4	[X]Anxiety disord unspecified (GMS)	1
[X]Recurrent severe episodes/reactive de	1	[X]Anxiety disorder, unspecified	202
[X]SAD - Seasonal affective disorder	21	[X]Anxiety hysteria	8
[X]SAD-Seasonl affectiv disord	15	[X]Anxiety neurosis	236
[X]Seasonal depressive disorder	3	[X]Anxiety reaction	275
[X]Seasonal depressive disordr	4	[X]Anxiety state	514
[X]Severe depressiv no psychot (GMS)	5	[X]Claustrophobia	15
[X]Severe depressive + psychot	1	[X]Generalized anxiety disord	1
[X]Severe depressive + psychot (GMS)	7	[X]Generalized anxiety disord (GMS)	11
[X]Severe depressive episode with psycho	215	[X]Generalized anxiety disorder	151
[X]Severe depressive episode without psy	1,215	[X]Mild anxiety depression	144
[X]Sgl epi,maj depres+psyc sym	3	[X]Mixed anxiety and depressive disorder	486
[X]Single epis/depress react	1	[X]Mixed anxiety/depressve dis (GMS)	1
[X]Single epis/psychog depress	1	[X]Needle phobia	210
[X]Single episode agitated depressn w'ou	1	[X]Other anxiety disorders	58
[X]Single episode major depression w'out	7	[X]Other mixed anxiety disord (GMS)	1
[X]Single episode of depressive reaction	1	[X]Other mixed anxiety disorders	3
[X]Single episode of major depression an	2	[X]Other phobic anxiety disord	1
[X]Single episode of masked depression N	1	[X]Other phobic anxiety disorders	3
[X]Single episode of psychogenic depress	1	[X]Other specif anxiety disord (GMS)	1
[X]Single episode of psychogenic depress	1	[X]Other specified anxiety disorders	6
[X]Single episode of psychotic depressio	10	[X]Panic attack	98
[X]Single episode of reactive depression	15	[X]Panic disorder [episodic paroxysmal a	57
[X]Single episode of reactive depressive	2	[X]Panic disorder with agoraphobia	19
[X]Single major depr ep, severe with psy	1	[X]Panic disorder with agrophobia	1
[X]Sngl episd/reactive depresn	3	[X]Panic disorder+agoraphobia	54

[X]Sngl episod/psychot depress	1	[X]Panic disorder+agrophobia	2
depression	3	[X]Panic episodic paroxysm anx (GMS)	5
depression, MNW, NFD	1	[X]Panic state	38
		[X]Phobia NOS	49
		[X]Phobic anxiety disorder, unspecified	7
		[X]Phobic anxiety disorders	32
		[X]Phobic anxiety disordr unsp (GMS)	4
		[X]Phobic state NOS	6
		[X]Simple phobia	16
		[X]Social neurosis	3
		[X]Social phobias	118
		[X]Specific (isolated) phobia	2
		[X]Specific (isolated) phobia (GMS)	1
		[X]Specific (isolated) phobias	75
		anxiety /ox	2
		anxiety autonomic situational /ox	19
		flying fear /ox	1
		phobia against flying recent going on	1
		pregnancy fear /ox	1

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Risk of incident cardiovascular events amongst individuals with depression and anxiety in east London

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Background

- Patients with anxiety and depression have an increased incidence of cardiovascular disease. It is unknown how the risk of myocardial infarction (MI) and stroke differs for patients with depression and anxiety and whether this risk varies by gender, ethnicity, deprivation, antidepressant use and cardiovascular co-morbidities.

Aim and hypotheses

- The aim of this study was to quantify differences in the risk of stroke or myocardial infarction (MI) among patients with depression or anxiety. We hypothesize that risk will be increased in patients with psychiatric conditions compared to those without and that increased risk can be further explained by sociodemographic and cardiovascular risk factors.

Methods

- 524,952 patients aged 30 and over were identified from the east London primary care database. Cox proportional-hazards regression was used to examine differences in the risk of incident MI and stroke between patients with and without diagnosed anxiety or depression between March 2005 and March 2015.

Table 1. Association between depression and MI/Stroke

Depression Cohort	Risk of MI		Risk of Stroke	
Psychiatric diagnosis	1.24	[1.08,1.42]	1.31	[1.01,1.69]
Age	1.07	[1.07,1.07]	1.07	[1.07,1.08]
Male gender (female ref)	2.77	[2.57,3.00]	1.41	[1.24,1.61]
South Asian (White ref)	1.83	[1.68,1.99]	1.18	[0.99,1.41]
Black African/Caribbean	0.52	[0.46,0.59]	1.32	[1.11,1.56]
Other ethnic group	0.80	[0.67,0.97]	1.09	[0.80,1.49]
Hypertension	1.18	[1.07,1.29]	1.49	[1.26,1.75]
Diabetes Mellitus	1.48	[1.34,1.64]	1.47	[1.22,1.77]
Hyperlipidemia	1.07	[0.98,1.17]	0.85	[0.72,1.01]
Current smoker	1.99	[1.83,2.15]	1.31	[1.10,1.56]
Antidepressant use	1.21	[1.09,1.34]	1.01	[0.82,1.24]
Townsend deprivation score	1.06	[1.04,1.09]	1.03	[0.99,1.07]

*** p<0.05 **p<0.01 ***p<0.0001**

Results

- Of 21,811 individuals with depression at baseline, 1.2% had MI and 0.4% had stroke during follow-up.
- Of 22,128 individuals with anxiety at baseline, 1.1% had MI and 0.3% had stroke during follow-up.
- Compared to patients without depression, patients with depression had an increased risk of MI and stroke after adjustment for confounding factors.
- No increase in MI and stroke risk was apparent for patients with anxiety after adjustment for confounding factors.
- Antidepressant use increased risk for MI but not stroke.

Table 2. Association between Anxiety and MI/Stroke

Anxiety Cohort	Risk of MI		Risk of Stroke	
Anxiety at baseline	1.11	[0.97,1.28]	1.10	[0.84,1.42]
Age	1.07	[1.07,1.07]	1.07	[1.07,1.08]
Male gender (female ref)	2.77	[2.56,2.99]	1.41	[1.24,1.60]
South Asian (White ref)	1.82	[1.67,1.98]	1.17	[0.98,1.40]
Black African/Caribbean	0.52	[0.46,0.59]	1.31	[1.11,1.55]
Other ethnic group	0.80	[0.66,0.96]	1.08	[0.79,1.48]
Hypertension	1.18	[1.07,1.29]	1.48	[1.26,1.75]
Diabetes Mellitus	1.49	[1.34,1.64]	1.47	[1.22,1.77]
Hyperlipidemia	1.07	[0.98,1.17]	0.85	[0.72,1.01]
Current smoker	1.99	[1.84,2.16]	1.32	[1.11,1.57]
Antidepressant use	1.25	[1.12,1.38]	1.06	[0.87,1.29]
Townsend deprivation score	1.07	[1.04,1.09]	1.03	[0.99,1.07]

*** p<0.05 **p<0.01 ***p<0.0001**

Conclusions

- Patients with depression, but not anxiety have an increased risk of MI and stroke after accounting for common cardiovascular risk factors.
- The association between mental health conditions and cardiovascular outcomes after adjustment for cardiovascular risk factors provides strong evidence on the nature of the link between mental health and cardiovascular events, and can be used to design interventions to reduce cardiovascular mortality among psychiatric patients.

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Figure 4.1.1 Poster basado en el articulo, presentado en el *General Adult Psychiatry Faculty Conference* en Londres en Octubre de 2015.

5. FACTORES DE RIESGO CARDIOVASCULAR EN PACIENTES CON PATOLOGÍA PSIQUIÁTRICA ATENDIDOS EN ATENCIÓN PRIMARIA

Las revisiones de literatura presentadas en el capítulo tercero muestran la asociación de las patologías psiquiátrica y cardiovascular. Sin embargo una de las labores que más dedicación exige a los médicos de familia, dentro de la atención a la patología cardiovascular, no es la asistencia a pacientes con eventos cardiovasculares sino el control de factores de riesgo cardiovascular. Además, como ya se ha mencionado anteriormente existen una serie de dificultades añadidas para una correcta atención de los problemas cardiovasculares que se presentan en pacientes con patología psiquiátrica.[11]

Algunos de los estudios presentados en la revisión bibliográfica sugieren que la incidencia de factores de riesgo cardiovascular en pacientes con patología psiquiátrica puede estar aumentada. Sin embargo esta evidencia es limitada para los distintos problemas psiquiátricos y los diferentes factores de riesgo cardiovascular, y por ello es difícil elaborar intervenciones clínicas basadas en los estudios disponibles. En el artículo que presento a continuación se observó a lo largo de diez años, si los pacientes con esquizofrenia, enfermedad bipolar, depresión, ansiedad, o trastornos de la personalidad, tenían un riesgo aumentado de desarrollar diabetes tipo II, hipercolesterolemia, hipertensión, hábito tabáquico, sedentarismo u obesidad. También se investigó si los antidepresivos, los antipsicóticos y el bajo nivel socioeconómico pueden explicar dicha asociación. Por último se observó si los factores de riesgo cardiovascular en estos pacientes se detectan a una edad más tardía. Este trabajo ha sido publicado en *European Psychiatry*.[74]

Cardiovascular risk factors among patients with schizophrenia, bipolar, depressive, anxiety, and personality disorders

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Key words: cardiovascular diseases, schizophrenia, antipsychotic agents, antidepressive agents, socioeconomic factors, cohort studies

Abstract:

Background: The evidence informing the management of cardiovascular risk in patients with psychiatric disorders is weak.

Methods: This cohort study used data from all patients, aged≥ 30, registered in 140 primary care practices (n=524952) in London to estimate the risk of developing diabetes, hypertension, hyperlipidemia, tobacco consumption, obesity, and physical inactivity, between 2005 and 2015, for patients with a previous diagnosis of schizophrenia, depression, anxiety, bipolar or personality disorder. The role of antidepressants, antipsychotics and social deprivation in these associations was also investigated. The age at detection of cardiovascular risk factor was compared between patients with and without psychiatric disorders. Variables, for exposures and outcomes, defined from general practitioners records, were analysed using multivariate regression.

Results: Patients with psychiatric disorders had an increased risk for cardiovascular risk factors, specially diabetes, with hazard ratios: 2.42(2.20-2.67) to 1.31(1.25-1.37), hyperlipidemia, with hazard ratios: 1.78(1.60-1.97) to 1.25(1.23-1.28), and obesity. Antidepressants, antipsychotics and social deprivation did not change these associations, except for smoking and physical inactivity. Antidepressants were associated with higher risk of diabetes, hypertension and hyperlipidemia. Antipsychotics were associated with a higher risk of diabetes. Antidepressants and antipsychotics were associated with lower risk of other risk factors. Patients with psychiatric conditions have later detection of cardiovascular risk factors. The interpretation of these results should acknowledge the lower rates of detection of risk factors in mentally ill patients.

Conclusions: Cardiovascular risk factors require special clinical attention among patients with psychiatric disorders. Further research could study the effect of antidepressants and antipsychotics on cardiovascular risk factors.

1. Introduction

Patients with psychiatric disorders have a shorter life expectancy, with cardiovascular disease being the major contributor to these premature deaths.(1, 2) However, the epidemiological evidence informing the management of cardiovascular risk (CVR) in these patients is still too limited in order to inform effective clinical interventions. This contributes to a poor control of CVR factors and poor cardiovascular outcomes.(3) Patients with psychiatric disorders often have an unhealthy lifestyle which is associated with and increased CVR.(4, 5) While the prevalence of some cardiovascular risk factors, such as hypertension and diabetes, have been studied recently in a number of systematic reviews for patients with specific diseases, i.e. depression or schizophrenia, the evidence is weaker for patients with other conditions such as anxiety or personality disorders.(6-10) These reviews highlight limitations in the some of the available evidence, including non-prospective study design, small sample size, and inadequate data on demographic and lifestyle factors. An association between antidepressants or antipsychotics, and a higher prevalence of CVR factors such as diabetes has been identified.(7, 11-14) Social deprivation is strongly associated with psychiatric conditions and with higher CVR as well.(15-17) However, the extent to which antidepressants, antipsychotics, and social deprivation contribute to the development of CVR factors among patients with different psychiatric disorders is unclear.(3) Many symptoms of psychiatric conditions, including cognitive impairment, together with other factors, such as the stigmatization of these patients, make difficult their access to health care.(2) This may result in later diagnoses and less effective management of CVR factors.

The first objective of this study is to estimate the risk of developing incident type 2 diabetes, hypertension, hyperlipidemia, active smoking, obesity, and physical inactivity, over a ten year period, for patients previously diagnosed with schizophrenia, bipolar disorder,

depression, anxiety or personality disorders. The second objective is to investigate the potential explanatory role of antidepressants, antipsychotics and deprivation in the association between each psychiatric condition and each CVR factor. The third objective is to compare the age at the time of diagnosis of each CVR factor, in patients with and without psychiatric disorders.

2. Methods:

The study conformed to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) study design recommendations.(18)

2.1 Study population

Data from the 524 952 patients living in three inner boroughs of east London (UK), registered with the local primary care surgeries, were used. Anonymized demographic and clinical data recorded in primary care electronic health records were extracted using EMIS web software from 140 of the 144 surgeries in the boroughs (four surgeries used a different computer system and were not included) for all patients aged 30 years and over in March 2015. Patients from that age category were selected because most cardiovascular events occur in patients over 30 and clinical guidelines suggest periodic screening for CVR factors in patients from the age of 40.(19, 20)

2.2 Variable definition

Sociodemographic variables included age, gender, and self-reported ethnic group. The Townsend score for social deprivation was also recorded.(21) Ethnicity was grouped into four categories: white, south Asian, black African/Caribbean and other. Individuals of mixed ethnicity were grouped with the relevant ethnic minority group. Clinical data included

routinely recorded diagnoses of schizophrenia, bipolar disorder, depression, anxiety, personality disorders, type 2 diabetes, hypertension, hyperlipidemia, obesity, and self-reported smoking status and physical inactivity. Given the large number of exposures and outcomes analysed, all clinical data were coded as binary variables. A systematic approach to accurately identify each psychiatric condition and CVR factor from patient records was used. Lists of terms (Read codes) used by primary care physicians were compiled for each psychiatric condition and CVR factor using the UK National Health Service Clinical Terminology Browser version 2 10-01-2013 (Appendix A). Data was also extracted on prescriptions of antidepressants and antipsychotic drugs according to their classification in the British National Formulary(22) (Appendix B). Obesity was defined by the record of body mass index >30. The medical records included terms reporting whether patients were smokers or nonsmokers. There were also terms reporting different frequency for physical activity, and patients were categorized accordingly: ≥3 sessions of exercise a week active, and <3 inactive.(23) There were only terms reporting the presence, but not the absence, of other CVR factors such as diabetes, psychiatric conditions, or prescribed drugs, and patients without these terms in their records were considered not to have them.

2.3 Statistical analysis

The risk of being diagnosed with type 2 diabetes, hypertension, hyperlipidemia, being a current smoker, obese, or physically inactive, between March 2005 and March 2015, was compared for patients with and without a diagnosis of schizophrenia, bipolar disorder, depression, anxiety, or personality disorder, at the beginning of that period. Patients with diagnosis of a CVR factor before the March 2005 were not included in the analysis for that specific outcome. When a CVR factor (i.e. obesity) had been recorded more than once during the follow up, only the first record in clinical notes was included in the analysis.

Cox regression models adjusted for potential confounders (age, gender, and ethnicity) were first used to estimate the associations of each psychiatric condition with each CVR factor. In a second step potential explanatory factors for the associations (prescription of antidepressants and antipsychotics before the 19th March 2005, and Townsend deprivation score), were included in the models. The age at the time of having each CVR factor recorded in patients with and without schizophrenia or other psychiatric disorder was compared using linear regression models adjusted for gender and ethnicity. The whole sample was treated as a single cohort, as patients were all living in the same area of London, where there is free access to health care for everyone, health care is standardized, and all patients were treated as independent within the cohort.

2.4 Ethical approval

All data were anonymised and managed according to the UK National Health Service information governance requirements. Ethical approval was not required for the use of routinely collected anonymised data in this observational study.

3. Results

A total of 524952 patients, with mean age 45.9 (SD: 13.9), were included in the study. The sociodemographic description of the cohort, the medications prescribed, and the CVR risk factors diagnosed in patients with each psychiatric condition, are presented in tables one and two.

	N (%)	Age Mean (SD)	Gender n (%)		Ethnicity n (%)					Depriva-tion Mean (SD)	Anti depressants	Anti psychotics
			Female	Male	White	South Asian	Black	Other	Un-known			
All cohort	524952 (100)	45.9 (13.9)	247528 (47.1)	277423 (52.8)	220079 (41.9)	144666 (27.6)	89186 (17.0)	32425 (6.2)	38596 (7.3)	5.2 (1.8)	37107 (7.1)	20498 (3.9)
Schizophrenia	2579 (0.5)	53.0 (13.1)	1014 (39.3)	1565 (60.7)	913 (35.4)	590 (22.9)	871 (33.8)	112 (4.3)	93 (3.6)	5.8 (1.7)	579 (22.5)	1336 (51.8)
Bipolar	705 (0.1)	52.2 (13.3)	399 (56.6)	306 (43.4)	369 (52.3)	133 (18.9)	140 (19.9)	30 (4.3)	33 (4.7)	5.5 (1.8)	209 (29.6)	330 (46.8)
Depression	21811 (4.1)	53.1 (13.6)	13777 (63.2)	8034 (36.8)	13436 (61.6)	3182 (14.6)	3155 (14.5)	869 (4.0)	1169 (5.4)	5.5 (1.7)	11149 (51.1)	3880 (17.8)
Anxiety	22128 (4.2)	52.7 (13.9)	13267 (60.0)	8861 (40.0)	13863 (62.6)	3507 (15.8)	2739 (12.4)	889 (4.0)	1130 (5.1)	5.4 (1.8)	9546 (43.1)	3579 (16.2)
Personality	1719 (0.3)	53.7 (13.2)	745 (43.3)	974 (56.7)	1209 (70.3)	155 (9.0)	194 (11.3)	72 (4.2)	89 (5.2)	5.6 (1.7)	590 (34.3)	383 (22.3)

Table 1. Characteristics of participants in the study

	Diabetes n (%)		Hypertension n (%)		Hyperlipidaemia n (%)		Smoking n (%)		Obesity n (%)		Physical inactivity n (%)	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
All cohort	474871 (93.7)	31942 (6.3)	438006 (89.8)	49688 (10.2)	320270 (66.3)	163049 (33.7)	242549 (71.7)	95692 (28.3)	389747 (79.7)	99010 (20.3)	72819 (23.4)	238450 (76.6)
Schizophrenia	1898 (81.1)	443 (18.9)	1915 (83.5)	377 (16.5)	865 (39.2)	1344 (60.8)	491 (44.9)	603 (55.1)	1251 (59.4)	856 (40.6)	573 (35.0)	1063 (65.0)
Bipolar disorder	565 (86.5)	88 (13.5)	550 (86.6)	85 (13.4)	247 (40.2)	368 (59.8)	164 (51.1)	157 (48.9)	351 (59.1)	243 (40.9)	145 (32.2)	306 (67.8)
Depression	18713 (91.1)	1827 (8.9)	16198 (86.1)	2611 (13.9)	8419 (48.2)	9039 (51.8)	4201 (57.4)	3111 (42.6)	13271 (73.7)	4749 (26.3)	3389 (28.4)	8530 (71.6)
Anxiety	19324 (91.8)	1716 (8.2)	16299 (85.9)	2670 (14.1)	8905 (50.1)	8883 (49.9)	4514 (60.5)	2943 (39.5)	14096 (75.3)	4615 (24.7)	3137 (26.7)	8617 (73.3)
Personality dis	1486 (90.9)	149 (9.1)	1344 (87.3)	196 (12.7)	677 (45.9)	799 (54.1)	359 (47.4)	399 (52.6)	1040 (65.6)	455 (30.4)	322 (31.5)	699 (68.5)

Table 2. Cardiovascular risk factors identified during study period among participants with different psychiatric disorders at study entry.

3.1 Association between psychiatric disorders and cardiovascular risk factors

The risk for CVR factors in patients with each psychiatric disorder is presented in table three. Patients with all psychiatric disorders had an increased risk of having an incident diagnosis of type 2 diabetes, with Hazard Ratios (HRs) ranging from 1.31 (1.25-1.37) for those with anxiety disorders to 2.42 (2.20-2.67) $p<0.001$ for those with schizophrenia. The risk of hyperlipidaemia was also increased for all patients with psychiatric disorders, with HRs

ranging from 1.25 (1.23-1.28), for those with anxiety disorders, to 1.78 (1.60-1.97) $p<0.001$ for those with bipolar disorder. Obesity was also associated with all psychiatric conditions, with HR ranging from 1.09 (1.06-1.12), for those with anxiety disorders, to 1.90 (1.67-2.15) $p<0.001$ for those with bipolar disorders. Patients with schizophrenia, depression and anxiety had an increased risk of hypertension.

3.2 Role of antidepressants, antipsychotics and social deprivation

The associations between psychiatric disorders and CVR factors remained significant after adjustment for antidepressants, antipsychotics and deprivation score (table three). Patients with schizophrenia, bipolar disorder, and depression had a higher risk of smoking only in the models adjusted for age, gender, ethnicity, antidepressants, antipsychotics and deprivation. Those with depression, bipolar, and personality disorders had an increased risk of physical inactivity only after adjustment for age, gender ethnicity, antidepressants, antipsychotics and deprivation (Table three).

An independent association was observed between the prescription of antidepressants and an increased risk of type 2 diabetes, with HRs ranging from 1.28 (1.23-1.33) to 1.35 (1.04-1.15), hypertension, with HRs ranging from 1.09 (1.05-1.12) to 1.11 (1.07-1.14), and hyperlipidemia, with HRs ranging from 1.05 (1.03-1.07) to 1.12 (1.10-1.14). However, the risk of smoking, obesity and physical inactivity was significantly lower among those who had been prescribed antidepressants. Patients who had been prescribed antipsychotics had an increased risk of type 2 diabetes but lower risk of hypertension, hyperlipidemia, smoking, obesity and physical inactivity (Table four).

	Diabetes	Hyper tension	Hyperlipi daemia	Smoking	Obesity	Physical inactivity
Schizophrenia						
Adjustment for age, gender and ethnicity	2.42 2.20-2.67	1.17 1.05-1.29	1.65 1.56-1.74	0.94 0.89-1.00	1.74 1.62-1.86	1.04 0.99-1.09
p	<0.001	0.003	<0.001	0.059	<0.001	0.114
Adjustment for age gender ethnicity antidepressants antipsychotics deprivation	2.14 1.94-2.37	1.17 1.05-1.30	1.67 1.58-1.77	1.94 1.83-2.07	1.84 1.71-1.98	1.21 1.15-1.27
p	<0.001	<0.003	<0.001	<0.001	<0.001	<0.001
Bipolar Disorder						
Adjustment for age, gender and ethnicity	1.96 1.59-2.43	1.12 0.90-1.39	1.78 1.60-1.97	0.98 0.88-1.10	1.90 1.67-2.15	1.08 0.98-1.18
p	<0.001	<0.298	<0.001	0.804	<0.001	0.105
Adjustment for age gender, ethnicity, antidepressants, antipsychotics and deprivation	1.68 1.36-2.08	1.12 0.91-1.39	1.78 1.60-1.97	1.78 1.59-1.99	2.01 1.77-2.28	1.27 1.16-1.39
p	<0.001	0.291	<0.001	<0.001	<0.001	<0.001
Depression						
Adjustment for age, gender and ethnicity	1,43 1.36-1.50	1.11 1.10-1.15	1.30 1.28-1.33	0.67 0.65-0.68	1.12 1.09-1.16	0.91 0.89-0.92
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Adjustment for age gender, ethnicity, antidepressants, antipsychotics and deprivation	1.22 1.16-1.29	1.07 1.02-1.11	1.28 1.25-1.31	1.20 1.17-1.23	1.20 1.16-1.24	1.08 1.06-1.10
p	<0.001	0.003	<0.001	<0.001	<0.001	<0.001
Anxiety						
Adjustment for age, gender and ethnicity	1.31 1.25-1.37	1.12 1.08-1.17	1.25 1.23-1.28	0.64 0.63-0.66	1.09 1.06-1.12	0.88 0.86-0.89
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Adjustment for age gender, ethnicity, antidepressants, antipsychotics and deprivation	1.14 1.08-1.20	1.09 1.05-1.14	1.23 1.20-1.26	0.99 0.97-1.02	1.14 1.11-1.18	1.00 0.98-1.02
p	<0.001	<0.001	<0.001	0.545	<0.001	0.771
Personality Disorder						
Adjustment for age, gender and ethnicity	1.56 1.32-1.83	1.08 0.94-1.25	1.50 1.40-1.61	0.96 0.89-1.03	1.51 1.38-1.66	0.99 0.93-1.06
p	<0.001	0.271	<0.001	0.231	<0.001	0.853
Adjustment for age gender, ethnicity, antidepressants, antipsychotics and deprivation	1.36 1.15-1.60	1.05 0.92-1.21	1.46 1.36-1.57	1.42 1.33-1.53	1.55 1.42-1.71	1.11 1.04-1.18
p	<0.001	0.459	<0.001	<0.001	<0.001	0.001

Table 3. Risk of developing CV Risk factors in patients with psychiatric conditions

	Diabetes	Hypertension	Hyperlipidaemia	Smoking	Obesity	Physical inactivity
Antidepressants						
Schizophrenia	1.35 1.04-1.15	1.11 1.07-1.14	1.12 1.10-1.15	0.15 0.14-0.15	0.91 0.89-0.94	0.72 0.71-0.73
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Bipolar dis.	1.34 1.29-1.39	1.10 1.07-1.14	1.12 1.10-1.15	0.15 0.14-0.15	0.91 0.89-0.93	0.72 0.71-0.73
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Depression	1.28 1.23-1.33	1.09 1.05-1.12	1.05 1.03-1.07	0.14 0.14-0.15	0.87 0.84-0.89	0.71 0.69-0.72
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Anxiety	1.31 1.26-1.36	1.09 1.05-1.12	1.07 1.05-1.09	0.15 0.14-0.15	0.88 0.86-0.91	0.72 0.71-0.73
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Personality dis	1.34 1.29-1.34	1.11 1.07-1.14	1.12 1.10-1.14	0.15 0.14-0.15	0.91 0.88-0.93	0.72 0.71-0.73
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Antipsychotics						
Schizophrenia	1.09 1.04-1.15	0.93 0.89-0.97	0.93 0.91-0.96	0.17 0.16-0.18	0.87 0.84-0.90	0.77 0.75-0.78
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Bipolar dis.	1.15 1.10-1.21	0.94 0.90-0.98	0.95 0.93-0.98	0.18 0.17-0.19	0.90 0.88-0.94	0.77 0.76-0.79
p	<0.001	0.002	<0.001	<0.001	<0.001	<0.001
Depression	1.15 1.10-1.21	0.94 0.90-0.97	0.95 0.93-0.98	0.18 0.17-0.19	0.91 0.88-0.94	0.78 0.76-0.79
p	<0.001	0.001	<0.001	<0.001	<0.001	<0.001
Anxiety	1.16 1.10-1.21	0.93 0.90-0.97	0.95 0.93-0.98	0.19 0.17-0.20	0.91 0.88-0.94	0.78 0.76-0.79
p	<0.001	0.001	<0.001	<0.001	<0.001	<0.001
Personality dis	1.16 1.11-1.21	0.94 0.90-0.98	0.96 0.94-0.98	0.19 0.18-0.20	0.91 0.88-0.94	0.78 0.76-0.79
p	<0.001	0.002	0.001	<0.001	<0.001	<0.001

Table 4. Risk of developing cardiovascular risk factors in patients taking antidepressants and antipsychotics.

Models adjusted for each psychiatric disease, age gender ethnicity, Townsend, antipsychotics and antidepressants.

3.3 Age at detection of CVR factors for those with and without psychiatric disorders

Smoking was diagnosed at a later age for all patients with psychiatric disorders, with age at detection 36.7 (36.7-36.8) for those without schizophrenia and 45.0 (44.2-45.8) $p<0.001$ for those with schizophrenia (Table five). Similarly, physical inactivity was diagnosed at a later age among all patients with psychiatric disorders, with age at detection 44.0 (43.9-44.1) for those without schizophrenia and 45.4 (44.6-46.2) for those with schizophrenia $p<0.001$, age 49.6 (48.8-50.4) $p<0.001$ for those with personality disorder and age 42.1 (42.1-42.2) for those with no personality disorder. Obesity was also diagnosed later in patients with schizophrenia and other psychiatric conditions except in bipolar disorder. Finally, hyperlipidemia was diagnosed at a later age for patients with depression, anxiety and personality disorders (Table five)

		DM	Hypertension	Smoking	Hyperlipidaemia	Obesity	Physical inactivity
Schizophrenia	N	52.4 52.2-52.6	52.8 52.7-52.9	36.7 36.7-36.8	47.0 47.0-47.1	44.0 43.9-44.1	42.1 42.1-42.2
	Y	49.3 48.1-50.6	52.3 51.1-53.6	45.0 44.2-45.8	46.9 46.3-47.6	45.4 44.6-46.2	48 47.7-48.9
	p	0.001	0.776	<0.001	0.665	0.005	<0.001
Bipolar	N	52.3 52.2-52.5	52.8 52-7-52.9	36.6 36.7-36.8	47.0 47.0-47.1	44.0 43.9-44.1	42.1 42.1-42.2
	Y	51.8 49.3-54.4	55.1 52.8-57.4	43.6 42.1-45.1	42.3 47.0-48.4	45.6 44.0-47.1	47.9 46.7-49.1
	p	0.167	0.285	<0.001	0.266	0.143	<0.001
Depression	N	52.2 52.0-52.3	52.7 52.6-52.8	36.6 36.6-36.7	46.9 46.8-47.0	43.8 43.8-43.9	41.8 41.8-41.9
	Y	54.7 54.1-5.2	54.4 54.0-54.9	41.8 41.6-42.1	49.4 49.1-49.6	47.7 47.3-48.0	49.9 49.7-50.2
	p	0.323	0.987	<0.001	<0.001	<0.001	<0.001
Anxiety	N	52.2 52.0-52.3	52.7 52.6-52.8	36.7 36.6-36.7	46.9 46.8-47.0	43.8 43.8-43.9	41.9 41.8-41.9
	Y	54.9 54.4-55.6	54.6 54.2-55.1	40.9 40.6-41.2	49.2 48.9-49.4	47.8 47.4-48.1	49.2 48.6-49.4
	p	0.005	0.267	<0.001	<0.001	<0.001	<0.001
Personality	N	52.3 52.2-52.5	52.8 52.7-52.9	36.7 36.7-36.8	47.0 47.0-47.1	44.0 43.9-44.1	42.1 42.1-42.2
	Y	54.5 52.8-56.2	54.9 53.1-56.6	44.0 43.0-44.9	50.2 49.3-51.0	47.8 46.6-48.9	49.6 48.8-50.4
	p	0.261	0.870	<0.001	<0.001	<0.001	<0.001

Table 5. Age at the time of recording of each CV Risk factor in patients with and without psychiatric disorder. P values for the differences observed in multivariate analysis. Y:Yes, N:No

4. Discussion

4.1 Summary of findings

Patients with psychiatric disorders were found to have an increased risk of having a new diagnosis of CVR factors, especially diabetes, hyperlipidemia, and obesity. The excess is risk of the majority of CVR facts amongst patients with psychiatric conditions could not be fully explained by antidepressants, antipsychotics and social deprivation. Exceptions included smoking and physical inactivity, where these variables had an important explanatory role.

Antidepressant use was independently associated with higher risk of diabetes, hypertension, and hyperlipidemia, and antipsychotic use were independently associated with a higher risk of diabetes, but both groups of drugs were associated with lower risk of other CVR factors. Patients with psychiatric conditions were found to have a later detection of CVR factors, particularly smoking and obesity.

4.2 Strengths and weaknesses

The data are derived from an almost complete population residing in a single contiguous geographical area, and not from selected individuals or organisations, which provides the least biased sampling frame. All patients were registered in the surgeries when the dataset was defined in March 2015, with all historic clinically relevant information available, which allowed for the accurate identification of prevalent and incident diagnoses and prescriptions. However, no data were available from patients who died, or left the surgeries between 2005 and 2015. By contrast with many previous articles, this study has a large number of cases and long follow up period, which improved statistical power and allowed for the observation of different CVR factors developing over ten years.(3) While some degree of residual confounding is probably affecting these results, it was possible to model a range of explanatory variables simultaneously, allowing the independent explanatory role of multiple factors to be assessed. The analysis of a high number of factors increases the possibility that some of the observed finding may not be true associations and the result of chance. However, it should be noted that most associations were consistent in the analyses for different psychiatric problems and the adjustment of different confounders. This study included data on prescription of antidepressants and/or antipsychotics but no data was available on medication compliance and dosage, specific drug type, or continuity of prescribing. Furthermore, all exposures and outcomes were coded as binary variables, even those that

have a natural continuous distribution such as smoking or physical activity; this is a limitation of this paper. Future studies may address the risk developing different degrees of each CVR in patients with psychiatric disorders. The lower screening rates for these CVR factor in patients with psychiatric disorders, together with the overdiagnosis of some psychiatric problems, especially depression, may have resulted in an underestimation of the associations investigated.(9, 24, 25) Nonetheless, the use of structured data entry templates, and clinical facilitation in the east London practices studied, enabled routine entry of high quality data using agreed code sets for recording CVR factors. The diagnoses of different psychiatric conditions, CVR factors, and the medication prescribed is routinely reviewed by local clinicians as part of their national Quality and Outcome Framework audit returns which provides further validation of data quality.(26)

4.3 Interpretation of results in relation to previous literature

The increased risk of some CVR factors, such as smoking, in patients with selected psychiatric conditions has been reported before.(5-10, 27-29) However, the comprehensive approach to the distribution of different major CVR factors among patients with a wide range of specific psychiatric conditions had only been presented by a small number of studies of limited quality.(3)

The potential for weight gain observed in patients taking antidepressants and antipsychotics may explain the increased risk of diabetes.(11, 12) Some antipsychotics, such as clozapine and olanzapine, are associated with high metabolic risk.(30) Antipsychotics work on the cerebral centers responsible of appetite and satiety. They disrupt the anorexigen signal to the hypothalamus and they can cause obesity by blocking dopaminergic receptors that affect eating behavior. Other central effects of antipsychotics that can result in weight gain include the increase of prolactin secretion, and sedation, which may affect weight via physical

inactivity. At a peripheral level, antipsychotics also block the muscarinic receptors localized in the beta-cells of the pancreas, decreasing plasma levels of insulin.(31) These mechanisms can lead to obesity, insulin resistance, and dyslipidemia during prolonged treatments.(30) Many patients, who developed the CVR factors of interest prior to the study period, and potentially prior to the psychiatric diagnosis, were not eligible for inclusion into the study. This may explain the inconsistent association between different psychiatric disorders and a first ever detection of smoking, and also the lower risk for some CVR factors, including obesity, smoking and lack of physical activity, among those who had taken antipsychotics and antidepressants. The positive effect of antidepressants and antipsychotics in the mental health of these patients may also result in some patients adopting a healthier lifestyle, having better access to health services, and subsequently experiencing better control of some CVR factors. This could also explain the association between psychiatric disorders and smoking which is only significant once the models are adjusted for use of antidepressants and antipsychotics. This study may also be observing the unintentional but positive effect of antidepressants on smoking behaviour,(32) or an unreported long term effects of these antidepressants and antipsychotics. It has been observed that studies reporting high prevalence of CVR factors among patients with psychiatric disorders are cited more often than those reporting a low prevalence.(33) The self-reporting of CVR factors, such as physical activity or smoking, may be poorer for patients with psychiatric conditions.(4, 34) The different approach of clinicians to patients with psychiatric conditions may also have resulted in the unequal recording of CVR factors.(35) These differences could explain the observed association between antipsychotics and higher rates of physical activity or lower rates of smoking, which may not be real. The delayed detection of some CVR factors in patients with mental health conditions may have been affected by the financial incentives offered to some UK based general practitioners for the recording of CVR factors for patients

with and without psychiatric conditions.(26) The later identification of CVR factors in patients with mental health conditions is also in line with a study that showed that these patients are less likely than the general population to receive annual CVR screening.(25) This study assumed that the date that each psychiatric condition and CVR was entered into the medical records was the true date of diagnosis. In UK primary care doctors tend to enter diagnostic data during or immediately after consultation. Therefore, it was considered that the date of record and the date of actual diagnosis would not have differed substantially. The heterogeneity between the different psychiatric conditions observed in this study should be acknowledged, as clinical relevance of each of them can be very different.

4.4 Clinical implications

Clinicians should consider frequent and long term monitoring of CVR factors for patients with mental health conditions. Patients with psychiatric disorders receive fragmented care and guidelines in different countries are not consistent when stating whether CVR should be approached by primary care or psychiatry services.(36) It appears essential that clinicians in both services agree on who should deliver this care, and work co-ordinately. Clinical guidelines mention that CVR is especially high for those with either serious mental health problems,(20) or for those with anxiety and depression.(19) However, our findings would support the enhanced management of CVR for patients with a wide variety of psychiatric disorders. The European guidelines for prevention of cardiovascular disease recommend checking for CVR factors male patients over the age of 40 and women over the age of 50.(19) Our results also show that after adjustment for gender, many patients with psychiatric conditions developed CVR factors from the age of 40. This would support screening for CVR in patients, both men and women, with psychiatric conditions from the age of 40. Future studies may address whether these CVR factors can be detected and effectively treated also in

patients under 40. Monitoring CVR alone is insufficient for improving health outcomes. Studies show that the interventions for reducing CVR in patients with psychiatric conditions can be effective, for example via smoking cessation, exercise, and lifestyle change.(37-39) Exercise is associated with maximum benefit from interventions that include 90 minutes of moderately intense aerobic exercise a week. In order to minimise CVR these interventions may need to be delivered shortly after the diagnosis

Special attention should be given to patients treated with antidepressants who were found to have a higher risk of diabetes, hypertension, and hyperlipidemia, and those on antipsychotics, who were found to have an increased risk of diabetes. Many factors contribute to the later detection and poor control of CVR factors in these patients, which ultimately can lead to poorer health outcomes.(2) Therefore, patients with psychiatric conditions require an especially proactive clinical approach, with clinicians from primary and secondary care working closely in conjunction with one another. The evidence base for clinical practice is primarily drawn from clinical trials, which in most cases have less than one year of follow up.(40-45) Further studies examining the long term effects on CVR factors of antidepressants and antipsychotics are required.

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Psychiatric disorders	Read Code(s)
Schizophrenic disorders	E10..
Bipolar affective disorder	Eu31.
Depressive disorder NEC	E2B.. Eu33.
Anxiety states	E200. E202. Eu41. Eu40. Eu411
Personality disorders	E21.., Eu340, Eu341., Eu21., Eu6..
Cardiovascular risk factors	
Hypertension	G2, G20% G24-G2z (excluding G2400 G2410 G24z1 and G27) Gyu2 Gyu20
Diabetes Mellitus	C10%
Tobacco consumption	131%
Hyperlipidaemia	44P.
BMI>30	22K.
Exercise grading	138..

Appendix A. Read codes used to define each psychiatric condition and CVR factor

Antidepressant drugs	
Tricyclic antidepressants	Amitriptyline Hydrochloride Clomipramine Hydrochloride Dosulepin Hydrochloride Doxepin Imipramine Hydrochloride Lofepramine Nortriptiline Trimipramine
Tricyclic-related antidepressants	Minaserin Hydrochloride Trazodone Hydrochloride
Monoamine-oxidase inhibitors	Phenelzine Isocarboxazid Tranylcypromine Moclobemide
Selective serotonin re-uptake inhibitors	Citalopram Escitalopram Fluoxetine Fluvoxamine Maleate Paroxetine Sertraline
Other antidepressant drugs	Agomelatine Duloxetine Flupentixol Mirtzapine Reboxetine Venlafaxine
Antipsychotic drugs	
First-generation antipsychotic drugs	Benperidol Chlorprmazine Hydrochloride Flupentixol Haloperidol Levopromazine Pericyazine Perphenazine Pimozide Prochlorperazine Promazine Hydrochloride Sulpiride Trifluperazine Zuclopenthixol Zuclopenthixol Acetate
Second-generation antipsychotic drugs	Amisulpiride Aripriprazole Clozapine Lurasidone Hydrochloride Olanzapine Paliperidone Quetiapine Risperidone

Appendix B. Drugs categorised as antidepressants and antipsychotics

6- DISCUSIÓN

Esta tesis incluye una amplia revisión bibliográfica donde se observó que existe evidencia del mayor nivel que muestra la asociación entre algunas patologías psiquiátricas y los factores de riesgo y problemas cardiovasculares. Dicha asociación se ha mostrado sobre todo en pacientes con depresión y esquizofrenia.

La primera revisión sistemática original que presento añade a la literatura disponible hasta el momento, prueba de la asociación de los trastornos de ansiedad con el riesgo aumentado de ictus.

Finalmente, en la segunda revisión sistemática que presento se observó que los pocos autores que han estudiado las estimaciones del riesgo cardiovascular en pacientes con patología mental severa no observaron diferencias, a excepción de la esquizofrenia, con las estimaciones en personas sin patología psiquiátrica. El escaso número de artículos, y las limitaciones de los métodos para estimar el riego a largo plazo pueden explicar los resultados de esta revisión. El estudio bibliográfico puso de manifiesto la escasa evidencia que hay sobre los factores que explican la asociación entre la patología psiquiátrica y cardiovascular.

Las observaciones en pacientes de atención primaria de Londres mostraron que la depresión y la ansiedad están asociadas con una incidencia aumentada de sufrir un ictus o un evento coronario agudo. Los factores de riesgo cardiovascular y el bajo nivel socioeconómico no explican completamente la asociación en el caso de la depresión, y en pacientes con ansiedad parecen más relevantes. También se observó que los pacientes con depresión o ansiedad padecen eventos cardiovasculares a una edad más temprana. Por último se observó en el estudio que el uso de medicación antidepresiva está asociado con un riesgo aumentado de patología coronaria independiente de otros factores de riesgo cardiovascular, el bajo nivel socioeconómico, y el efecto que la propia depresión o ansiedad.

El estudio en que establezco el posible riesgo de desarrollar factores de riesgo cardiovascular mostró que los pacientes con depresión, ansiedad, esquizofrenia, enfermedad bipolar, y trastorno de personalidad tienen un riesgo aumentado de desarrollar factores de riesgo cardiovascular especialmente diabetes, hiperlipidemia, y obesidad. La medicación antidepresiva, antipsicótica y el bajo nivel socioeconómico mostraron una escasa relevancia en dichas asociaciones. Se encontró además una asociación entre los antidepresivos y un riesgo elevado de diabetes, hipertensión e hiperlipidemia. Los antipsicóticos se asociaron con un mayor riesgo de diabetes. Tanto los antidepresivos como los antipsicóticos estaban relacionados con una menor incidencia de otros factores de riesgo. Finalmente, se observó que los factores de riesgo cardiovascular se detectan más tardíamente en pacientes con enfermedades psiquiátricas.

6.1 Implicaciones para la práctica clínica

La evidencia sobre las asociaciones entre los problemas de salud mental y cardiovascular sigue siendo muy desigual. Esto complica la elaboración de guías de práctica clínica que propongan intervenciones específicas, factibles, y eficaces para reducir la incidencia de eventos cardiovasculares en pacientes con problemas psiquiátricos. Mientras que en algunos casos las guías de práctica clínica sobre problemas psiquiátricos ignoran completamente la patología cardiovascular, en otros casos proponen intervenciones preventivas y seguimientos poco compatibles con las peculiaridades de estos pacientes, y de difícil realización con los recursos disponibles actualmente.[37, 75]

De todos modos, los clínicos deben reconocer que cuando atienden a un paciente con un problema psiquiátrico se trata de una persona con un riesgo cardiovascular incrementado. Este no es sólo el caso de pacientes con patología psiquiátrica severa, como la esquizofrenia,

sino también de pacientes con trastornos que tradicionalmente se han considerado más benignos como la ansiedad.

En pacientes psiquiátricos sin síntomas cardiovasculares se puede recomendar que los clínicos tengan una actitud proactiva y busquen un control estricto de todos los factores de riesgo cardiovascular.

En paciente con síntomas de posible patología cardiovascular, la presencia de problemas mentales en los antecedentes debe alertar al clínico de la mayor posibilidad de estar atendiendo a un enfermo que sufre un evento cardiovascular agudo. Este hecho puede resultar especialmente útil en atención primaria donde muchos pacientes acuden con problemas cardiovasculares paucisintomáticos.

6.2 Implicaciones para investigación futura

Existen todavía áreas de interés donde falta información sobre las asociaciones entre la patología psiquiátrica y cardiovascular. Estas áreas de conocimientos limitados impiden el desarrollo de intervenciones preventivas y clínicas que puedan reducir eficazmente el riesgo cardiovascular de los pacientes con problemas de salud mental.

Mientras que algunas enfermedades como la depresión han recibido mucha atención por parte de los investigadores, el riesgo cardiovascular en pacientes con otros problemas, como la enfermedad bipolar o los trastornos de personalidad, necesita ser más estudiado en el futuro. Además, la contribución de cada factor de riesgo individual a la mayor incidencia de eventos cardiovasculares sigue sin estar bien definida; algunos factores como la obesidad o la diabetes parecen necesitar más atención que otros.[76, 77]

Por otro lado el riesgo cardiovascular puede cambiar con la historia natural del problema psiquiátrico y puede asociarse, por ejemplo, con el tiempo transcurrido desde el diagnóstico o la iniciación del tratamiento, el número de episodios agudos, hospitalizaciones, intentos de

suicidio o la institucionalización del paciente.[78] También, aunque se haya establecido la asociación entre grandes grupos de problemas psiquiátricos y la patología cardiovascular, la evidencia es escasa sobre el riesgo cardiovascular en pacientes con diagnósticos psiquiátricos específicos, como por ejemplo distintos tipos de trastornos de ansiedad. De igual modo, hay una información escasa acerca del riesgo que tienen los pacientes con problemas psiquiátricos de padecer ciertos eventos cardiovasculares más específicos como la angina, distintos subtipos de ictus, o sobre el resultado final de cada uno de ellos, por ejemplo su tasa de mortalidad o discapacidad.

La naturaleza de la asociación entre las enfermedades psiquiátricas y cardiovasculares sigue siendo incierta. Aunque los factores de riesgo cardiovascular, el bajo nivel socioeconómico, y la medicación psiquiátrica, pueden estar implicados en esta asociación, no parecen explicarla completamente. Estudios futuros pueden abordar el potencial papel explicatorio de mecanismos biológicos o explicaciones multifactoriales para la asociación entre patologías psiquiátricas y cardiovasculares.[27]

Uno de los factores modificables que puede explicar la asociación entre los problemas mentales y cardiovasculares, de especial relevancia para los investigadores clínicos, serían las desigualdades de atención sanitaria que sufren estos pacientes. Aunque hay estudios que han observado que los pacientes con problemas de salud mental reciben una peor atención primaria a sus problemas cardiovasculares, estas diferencias, y el efecto que tienen en la incidencia de patología coronaria e ictus, se conocen aún poco.[79, 80] Corresponde a los investigadores clínicos de atención hospitalaria el estudio detallado de las desigualdades que estos pacientes puedan sufrir en el manejo de problemas cardiovasculares agudos, y el efecto clínico de dichas desigualdades, que también se han observado, en un número limitado de estudios.[81] Es fundamental tener una información correcta y adecuada en este terreno para

poder desarrollar modelos de atención que realmente reduzcan el riesgo cardiovascular de estos pacientes.[82]

Otro factor que puede explicar la asociación de patología mental y cardiovascular, y que requiere ser estudiado en el futuro, es la medicación empleada en estos pacientes, en concreto los antidepresivos y los antipsicóticos. Los ensayos clínicos que se incluyen en las revisiones sistemáticas en las que se apoya la práctica clínica, tiene algunas limitaciones como es en muchos casos el bajo tamaño muestral, la inclusión de participantes que son distintos a los pacientes reales, y el seguimiento durante un tiempo que rara vez supera los dos años.[83-85] Estudios observacionales con tamaños muéstrales y seguimiento superior al de los ensayos clínicos medios han observado efectos asociados a la medicación psiquiátrica que no se habían encontrado en estudios experimentales.[86, 87] Estos resultados que en algunos casos muestran efectos adversos negativos, como una mayor mortalidad, en otros muestran efectos positivos, como una reducción del tabaquismo, necesitan estudiarse con mayor profundidad. El desarrollo de métodos estadísticos que permitan inferir causalidad partir de estudios observacionales es necesario para llevar adelante estos estudios.[88] Dichos métodos son especialmente importantes ahora que grandes bases de datos clínicos se han puesto a disposición de los investigadores y muchas asociaciones posiblemente causales que no se pueden ver en ensayos clínicos se van a poder estimar en estudios observacionales.

Los estudios futuros podrían abordar también las pautas terapéuticas específicas, tanto para el control de los factores de riesgo cardiovasculares en prevención primaria como en prevención secundaria, tal vez de mayor sencillez, que deben ser empleadas en estos pacientes. Las personas con patología psiquiátrica pueden necesitar aproximaciones terapéuticas diferentes, combinaciones de medicamentos, priorización de algunas intervenciones sobre otras, o criterios de control distintos.

También es necesario conocer en profundidad la experiencia que tienen los pacientes psiquiátricos, y los clínicos que los atienden, a la hora de abordar factores de riesgo y enfermedades cardiovasculares. En algunos casos, los clínicos de atención primaria pueden sentirse incómodos al tratar a los pacientes con problemas psiquiátricos. Esto puede deberse a su experiencia limitada con determinadas patologías, a los recursos de que se dispone, incluyendo el escaso tiempo por paciente, o a lo intimidante que algunas de estos personas resultan. La estigmatización de la patología mental es común entre el público en general y también entre los clínicos.[11] Los pacientes pueden sentir que su médico toma sus síntomas físicos menos en serio una vez que revelan su diagnóstico psiquiátrico. Otra barrera a la atención eficaz es que el clínico subestime la capacidad del paciente para cooperar en el tratamiento médico. Tal perspectiva puede conducir al "nihilismo terapéutico", donde no se ofrecen medidas preventivas o tratamientos eficaces a los pacientes. Todos estos factores, aunque difíciles de cuantificar son importantes en el manejo eficaz de la patológica cardiovascular, y están escasamente estudiados. Se necesitan por tanto nuevos estudios de investigación cualitativa que aborden este tema.[13]

En la atención a pacientes con problemas mentales es especialmente relevante la presencia y la intervención de cuidadores, normalmente familiares, que son fundamentales en el tratamiento de problemas físicos. Pero la relevancia del apoyo social y familiar también está sin estudiar y su importancia en clínica, es incierta.

También se necesitan estudios sobre la organización de la asistencia sanitaria que se da a estos pacientes. No está claro qué clínico es el que está mejor situado en cada momento de la enfermedad mental para controlar los factores de riesgo o la patología cardiovascular de estos pacientes. El papel de médicos y enfermeros tanto de atención primaria como de psiquiatría debe ser estudiado para ofrecer a estos pacientes un manejo eficaz de sus problemas cardiovasculares.

Una mejor prevención y un tratamiento más eficaz de la patología cardiovascular en los pacientes con problemas mentales deberían resultar también en un ahorro de recursos sanitarios que a día de hoy se están empleando para prevenir ineficazmente o para tratar problemas cardiovasculares que podrían haberse evitado. En el futuro, estudios de coste efectividad podrían abordar el posible ahorro económico que supondría el control y prevención de factores de riesgo y eventos cardiovasculares, basado en una evidencia más fuerte y más eficaz.

Aunque los datos epidemiológicos y los resultados de estudios cualitativos sean aún muy mejorables, los estudios disponibles permiten plantear ensayos clínicos que prueben intervenciones de cribado o manejo de factores de riesgo cardiovascular en pacientes con problemas psiquiátricos. La realización de dichos estudios no solo podría informar la práctica clínica sino que pondría de manifiesto algunos factores prácticos que dificultan la atención médica a estos pacientes y que los clínicos deberán tener en cuenta si se quiere realmente reducir su riesgo cardiovascular y mejorar su supervivencia.

Los investigadores que desarrollen herramientas en el futuro para estimar el riego cardiovascular a largo plazo, deben considerar la fuerte asociación entre la patología mental y cardiovascular. Problemas como la esquizofrenia o la ansiedad pueden ser tan predictivos de un ictus o un evento coronario como los factores de riesgo tradicionales. Por tanto, la presencia de antecedentes psiquiátricos en la historia de un paciente puede servir para estimar con mayor exactitud el riesgo que tenga de sufrir un evento cardiovascular a largo plazo, e informar así medidas preventivas.

Finalmente, la mayoría de los estudios sobre patología cardiovascular en personas con problemas psiquiátricos se han realizado en países desarrollados. La epidemiología y el manejo de problemas cardiovasculares en el contexto de la patología mental en los países en

desarrollo, que puede tener diferencias relevantes, es en gran parte desconocido y requiere ser abordado también en nuevos estudios.

Cualquier investigación futura que aspire a aportar una información de la máxima calidad requiere estar estructurada por unos valores éticos profundos y bien definidos. Los investigadores que aborden en el futuro los problemas de salud cardiovascular entre los pacientes con patología psiquiátrica, y que terminaran por encontrar soluciones eficaces para estos pacientes, deben buscar y trabajar en virtudes que incluyen la disciplina, la creatividad, la capacidad de pensar críticamente, la compasión y la prudencia. Este posicionamiento ético tan necesario para dar a la investigación clínica su mayor nivel requiere una reflexión profunda y dialogada sobre la naturaleza del bien que se persigue hacer en los estudios.[15, 89, 90]

6.3 Conclusiones de la tesis

1- El análisis de la bibliografía muestra una asociación entre algunas patologías psiquiátricas, factores de riesgo y problemas cardiovasculares. El riesgo de ictus esta aumentado un 25% en pacientes con trastornos de ansiedad. No hay evidencia de que el riesgo cardiovascular estimado a largo plazo sea mayor para los pacientes con enfermedad mental severa.

2- La depresión y la ansiedad están asociadas con una incidencia aumentada de eventos cardiovasculares agudos, que se presentan además a una edad más temprana. Los factores de riesgo cardiovascular y el bajo nivel socioeconómico podrían explicar parcialmente estas asociaciones. Los antidepresivos tienen una asociación independiente con un riesgo aumentado de patología cardiovascular.

3- Los pacientes con depresión, ansiedad, esquizofrenia, enfermedad bipolar, y trastorno de personalidad tienen un riesgo aumentado de tener factores de riesgo cardiovascular, que además se detectan a una edad más tardía. Los antidepresivos, antipsicóticos, y el nivel socioeconómico no explican dichas asociaciones. Estos dos grupos de fármacos se asocian con un riesgo elevado de desarrollar algunos factores de riesgo pero con un riesgo disminuido para desarrollar otros.

4- La evidencia disponible en la literatura y aportada por esta tesis es suficiente para recomendar el control estricto de factores de riesgo cardiovascular en clínica para todos aquellos pacientes con historia de depresión, ansiedad, esquizofrenia, enfermedad bipolar, o trastornos de personalidad.

Conclusions of this thesis

1- The analysis of the literature shows an association between some psychiatric disorders, cardiovascular risk factors and cardiovascular diseases. The risk of stroke is increased by 24% in patients with anxiety disorders. There is no evidence that the estimated long-term cardiovascular risk is higher for patients with severe mental illness.

2 - Depression and anxiety are associated with an increased incidence of acute cardiovascular events, which also occur at an earlier age in these patients. Cardiovascular risk factors and low socioeconomic status may partially explain these associations. Antidepressants have an independent association with an increased risk of cardiovascular disease.

3- Patients with depression, anxiety, schizophrenia, bipolar disorder, and personality disorder are at increased risk of having cardiovascular risk factors, which are also detected at a later age. Antidepressants, antipsychotics, and socioeconomic status do not explain these associations. Antidepressants and antipsychotics are associated with a higher risk of developing some risk factors but with a lower risk of developing others.

4- The available evidence in the literature, and provided by this thesis, is sufficient to recommend the strict control of cardiovascular risk factors for all patients with a history of depression, anxiety, schizophrenia, bipolar disorder, or personality disorders.

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